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VOLUME 81 NUMBER 4

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TEMPORAL ARTERITIS

Review of the Literature and Report of Five Additional Cases

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BENIGN arteritis and periarteritis of the temporal arteries was first described as a distinct clinical entity in 1932 by Horton, Magath, and Brown.[1] Since this time there have been reported in the literature 43 cases which seem to fall into the category of temporal arteritis. This disease is characterized by systemic symptoms of fever, anorexia, malaise, loss of weight and weakness; and local symptoms consisting of tender, swollen, nodular and thrombosed temporal arteries, with severe throbbing headache. Edema around the involved vessels is common. Pain in the adjacent structures, such as the scalp, face, jaws, eyes and temporomandibular joints, is also seen fairly constantly. Blindness has been a distressingly frequent complication of the disease. Some investigators, notably Cooke and his co-workers[2] and Chasnoff and Vorzimer,[3] have suggested that the disease is neither as benign nor as localized as was formerly thought. In order to evaluate this entity more accurately the essential data of all the reported cases were collected for critical analysis.

The fact that the disease is not as uncommon as the paucity of reported cases would indicate is suggested by the fact that Horton and Magath[4] were able to collect 7 cases by 1937 and Cooke and his associates[2] reported 7 cases seen in a four year period. Several other unreported cases are known to the authors.[5] Two cases here reported have been

Read before the Bangor Medical Club, Jan. 24, 1947.

From the Departments of Medicine and Pathology, Tufts College Medical School, Post-Graduate Division.

1. Horton, B. T.; Magath, T. B., and Brown, G. E.: Proc. Staff Meet., Mayo Clin. **7**:700-701 (Dec. 7) 1932; Arteritis of Temporal Vessels: Previously Undescribed Form, Arch. Int. Med. **53**:400-409 (March) 1934.

2. Cooke, W. T.; Cloake, P. C. P.; Govan, A. D. T., and Colbeck, J. C.: Quart. J. Med. **15**:47-76 (Jan.) 1946.

3. Chasnoff, J., and Vorzimer, J. J.: Ann. Int. Med. **20**:327-333 (Feb.) 1944.

4. Horton, B. T., and Magath, T. B.: Proc. Staff Meet., Mayo Clin. **12**:548-553 (Sept. 1) 1937.

5. (*a*) Heusner, A. P.: Personal communication to the authors. (*b*) Wilson, S.: Personal communication to the authors.

seen at the Eastern Maine General Hospital within a six month period. Three additional cases seen at the Joseph H. Pratt Diagnostic Hospital in Boston are briefly reported. All 5 cases fulfil the essential criteria of the disease entity. This brings the total of reported cases to 48.

REPORT OF CASES

CASE 1[6].—*History.*—C. M., a 73 year old housewife, was admitted to the hospital on July 6, 1946 because of blindness in the left eye. She had been well, except for chronic arthritis of mixed type, until two months before admission, when a steady throbbing headache developed over both temples and across the forehead. This had been associated with "swelling and redness of the veins of the forehead." She had noticed also that these "veins" were nodular and pursued a tortuous course. The nodules had been particularly sore and tender. Redness and swelling were present, extending about 1 cm. to either side of the "veins" all along their course. The aching had also been behind the eyes, in the eyeballs and over the upper part of the face. Treatment for "sinus trouble" had not afforded relief. There had been no hemicrania, nausea, vomiting, rhinorrhea or postnasal discharge. There was no swelling of the face or stiffness of the temporomandibular joint.

One week before admission she noticed "black spots" before the eyes, especially on the left side. Two days before admission on awakening there seemed to be a "black cloud" before her left eye. This cleared up in about an hour. The day before admission on awakening there seemed to be the same cloud over the temporal aspect of the left visual field, which also subsided in about an hour. Throughout the remainder of each day her vision seemed normal. On the day of admission she was unable to see anything with the left eye.

During the week prior to admission the headache had become much less severe and persisted only as a dull nagging bitemporal ache. She had lost about 20 pounds (9 Kg.) in weight during the present illness. She also knew that she had been having a low grade fever with a temperature up to "around 100 degrees" during this illness. Her appetite was poor.

The past history and review of systems were noncontributory. The mother and a brother had died many years previously of tuberculosis.

Examination.—Examination showed some evidence of recent loss of weight. The temporal arteries showed marked tortuosity, slight swelling and moderate nodularity. They were slightly tender to touch, and the nodules were especially tender. Compression of the arteries at their origin seemed to relieve the headache. There was no edema or redness of the skin at this time, but it was somewhat indurated. There was no tenderness of the mastoids or sinuses. The pupils were unequal, the left pupil measuring approximately 4 mm. in diameter and the right pupil 3 mm. Only the right pupil reacted to light and both reacted in accommodation. The ophthalmoscopic examination of the left eye revealed that the media were clear; the retina appeared grossly normal and the nerve head, which was faintly yellow, was fairly well outlined, especially in the temporal half, but without physiologic cupping. The arteries were narrow and tortuous, with a widened central light band. The size proportion of arteries to veins was approximately 1 to 3. The veins were somewhat full, and quite tortuous and showed segmentation in some areas, giving the appearance of broken columns of blood. No cherry red spot was seen and the macula appeared normal. There were four small blotlike

6. This case is reported with the permission of Dr. Robert Feeley and Dr. Robert McQuoid.

hemorrhages about half disk size situated about 2 disk diameters from the disk. There were sheaflike light areas over the veins in two places. The "sheaf" was constricted at the vessel and flared out at right angles on each side. Arteriovenous nicking was present but minimal. The findings on the right were essentially the same, except that there were only two small hemorrhages and the blood vessel changes were slightly less prominent. Vision was entirely absent in the left eye; with glasses it was normal in the right eye.

Examination of the oral cavity revealed edentulous gums and no evidences of inflammation. The tongue showed a scant coat and was slightly reddened. The jaws opened to admit two fingers vertically between the upper and lower incisors of her dentures. No cervical adenopathy or lymphadenopathy elsewhere was noted. The chest was clear to percussion and auscultation. The heart was of normal size and shape to percussion. The heart sounds were of good quality and no murmurs were heard. The abdomen and extremities were normal. Results of neurologic examination were entirely within normal limits.

Roentgen studies of the sinuses, skull and upper part of the gastrointestinal tract showed them to be normal. A roentgenogram showed that the chest was normal except for moderate sclerosis in the aortic arch.

Laboratory Examination.—Two voided specimens of urine were normal on routine analysis except for frequent red blood cells in the sediment of one. A catheterized specimen showed only a few red cells in the sediment. Blood studies showed 9 Gm. of hemoglobin per hundred cubic centimeters; red blood cells numbered 3,600,000 per cubic millimeter; white blood cells, 9,100 with a normal differential count and 0 to 2 per cent eosinophils. The nonprotein nitrogen was 42 mg per hundred cubic centimeters. Blood culture showed no growth. The reaction to the Kahn and Hinton tests of the blood was negative as was that of the spinal fluid to the Kolmer-Wassermann test. Lumbar puncture yielded clear and chemically normal spinal fluid under an initial pressure equivalent to 130 mm. of water. The cell count was 3 lymphocytes and 8 red blood cells per cubic millimeter and the protein was 35 mg. per hundred cubic centimeters. Erythrocyte sedimentation rate showed a rapid fall to 33 mm. in twenty minutes on three occasions, each reading also being 33 mm. at the end of an hour. Three weeks after admission it fell to 26 mm. in twenty minutes and 28 mm. at the end of an hour (Cutler method).

Treatment and Course.—The course in the hospital was at first uneventful. The headache was easily controlled by the administration of 10 grains (0.65 Gm.) of acetylsalicylic acid twice daily. On the third day in the hospital, she began to see "black spots" before the right eye. These lasted only fifteen minutes and subsided, but they kept recurring. Examination of the eyes revealed no change. The temperature ranged from 98 to 100 F. and the pulse rate from 68 to 90 beats per minute; the respirations were normal. Treatment consisted of amylnitrite inhalations four times daily and administration of nicotine acid 50 mg. four times daily. With this treatment she stated that she felt better. Ferrous sulfate, 2 grains (0.13 Gm.), three times daily, was given for the anemia. Despite treatment she lost an additional 10 pounds (4.5 Kg.) in the first two weeks of her hospital stay. During the entire second week her temperature remained normal. On the fifteenth day in the hospital she became totally blind in both eyes. She was unable to perceive even bright light. Examination revealed no changes except that the vascular changes in the right eye had gradually become more prominent. The broken columns of blood giving the segmented appearance to the veins were not seen again after the first two or three days. A few more hemorrhages, similar to those described, appeared in both eyes during her hospitalization. By the twenty-fifth day in the hospital, when she was discharged, she was just able to detect a bright light shown directly in either

eye. The headache had entirely disappeared. Ophthalmoscopic examination was unchanged. The temperature, after the onset of the total blindness, once again took a swinging course, going as high at 100 F. in the afternoon. At the time of discharge she had lost a total of 40 pounds (18.1 Kg.).

Follow-up Study.—This study four months after her admission to the hospital revealed that she had continued to have fever, malaise and anorexia for about a month after discharge. She had lost an additional 10 pounds of weight, making the total loss 50 pounds (22.7 Kg.). More recently she had been asymptomatic except for the blindness, which had not improved. The headache did not recur. About three months after discharge severe cystitis developed with urethral stricture and infection of the neck of the bladder. Treatment with sulfonamide compounds was started but had to be stopped because of nausea and vomiting. Urethral dilatation and irrigations of the bladder with silver nitrate cleared up these symptoms satisfactorily. She also had some reactivation of the arthritic symptoms. Examination revealed dilated, equal and immobile pupils. Ophthalmoscopic examination revealed that the nerve heads were pale and had a definite yellowish hue. The arteries showed sclerosis consistent with her age, the veins were normal, and there was slight arteriovenous compression. No hemorrhages were seen. The results of the remainder of the physical examination were unchanged.

Six months after discharge from the hospital and eight months after the onset of the disease she was seen again. She had remained well since her last visit. The mild arthritic pains were easily controlled by salicylates. With loss of sight her appetite remained poor and she failed to gain weight. She moved about little because of her poor vision. Vision had improved slightly, especially on the left; she could now distinguish grossly between light and dark without the light being shown directly into the eyes. Examination revealed that the left pupil was slightly smaller than the right and seemed to have some tone. The right pupil remained dilated and immobile. The nerve heads now showed mottling with almost black pigment over the lower halves. Otherwise observations were unchanged. Treatment since discharge from the hospital has been with administration of large doses of vitamins B complex and C.

CASE 2[7].—*History.*—B. W., a 64 year old housewife, entered the hospital on Aug. 6, 1946 complaining of pain across the forehead. She had been well until twelve weeks before admission, when she noticed a mild bilateral frontal headache. This was gradually progressive in severity and was only temporarily relieved by the usual analgesics. She described the pain as a severe throbbing ache concentrated at the temples. It seemed superficial and the skin over the temples and upper part of the forehead was sensitive to touch, especially along a swollen and nodular "vein" on each side. There was no hemicrania, nausea, vomiting, rhinorrhea or postnasal discharge. For ten days prior to admission she had had difficulty opening and closing her mouth because her "jaws seemed to stick." She was unable to open her mouth more than one fingerbreadth. For the past week the skin of the upper third of the face seemed puffy, especially about the right eye. There had been smarting pains in the eyeballs, especially on movement of the eyes. This was more marked on the right than on the left. The eyes seemed more comfortable closed and in a darkened room. She had felt slightly feverish throughout her illness but had not taken her temperature. She thought she had lost a few pounds in weight.

The past history, family history and review of systems were noncontributory.

Examination.—Examination revealed a well developed and well nourished white woman complaining of severe headache. The skin was clear and not flushed. There

7. Dr. Henry C. Knowlton permitted us to report this case.

was evidence of some recent loss of weight. The temporal arteries on both sides were swollen, firm and tortuous. There were multiple small nodules 2 or 3 mm. in diameter along the course of the arteries, usually at a turn in their tortuous course. Redness and nonpitting edema extended about 1 cm. to each side of the arteries along their entire course anteriorly. This whole area was tender to touch, especially over the nodules, where the tenderness was exquisite. Tenderness seemed to increase toward the origin of the arteries and was maximum over the temporomandibular joints. There was no tenderness over the mastoids or sinuses. The pupils were equal, round and regular and reacted well to light and in accommodation. The scleras and conjunctivas were clear. There was constant lacrimation of the right eye. The lids were voluntarily kept partly closed. Ophthalmoscopic examination revealed clear media and normal-appearing retinas. The vessels were normal and the nerve heads well outlined. There were no hemorrhages, exudates or arteriovenous nicking. Examination of the oral cavity was impeded by the inability of the patient to open her mouth more than 2.5 cm. between the upper and the lower incisors. No pharyngeal or tonsillar inflammation could be seen. There was slight nonpitting edema with redness of the upper third of the face, especially on the lateral aspects of the mandibular angles and extending up over the upper part of the forehead; this was more noticeable on the left. Cervical lymph nodes could not be palpated and adenopathy was not found elsewhere. Motion of the neck was normal. The pulmonary fields were clear to percussion and auscultation. The heart showed a normal rate and rhythm, with a grade pulmonic systolic murmur. The blood pressure was 150 mm. of mercury systolic and 80 mm. diastolic. No masses or viscera were palpated in the abdomen. There was a well healed appendectomy scar in the right lower quadrant. The extremities were normal. Cranial nerve function, reflexes and motor and sensory power were all normal.

Roentgen examination of the chest and temporomandibular joints showed no abnormalities. Roentgenograms of the anterior lower teeth showed moderate alveolar absorption but otherwise these teeth were normal; the remaining teeth were absent.

Laboratory Examination.—A catheterized specimen of urine was normal on routine analysis. The hemoglobin was 10.4 Gm. per hundred cubic centimeters; the red blood cells numbered 3,550,000 per cubic millimeter; the white blood cells, 11,000, with a normal differential count. No more than 4 per cent eosinophils were seen on any one count. The erythrocyte sedimentation rate was 18 mm. in 20 minutes and 29 mm. in 60 minutes (Cutler). Kahn and Hinton tests of the blood gave negative results. Blood nonprotein nitrogen was 30 mg. per hundred cubic centimeters.

Treatment and Course.—During hospitalization the temperature took a swinging course between 98.6 and 100 F., reaching 99 F. just before discharge, after a thirteen day stay in the hospital. The pulse rate varied from 90 to 120 beats a minute. The respiratory rate was normal. The patient usually required three 1/8 grain doses (0.008 Gm.) of morphine sulfate per day to control her headache. On the morning of the second day she complained of being unable to see with the right eye. Her vision returned to normal in a few hours, however, and the transient blindness did not recur. She insisted on having the room darkened and spent most of her time lying in bed with her eyes closed though not sleeping. She ate poorly and complained that eating hurt her at the temporomandibular joints.

A diagnosis of bilateral temporal arteritis was made on admission and symptomatic therapy was advised. The hospital course, however, seemed to indicate that some more active measures for the relief of pain would be required. She was seen, therefore, on the sixth hospital day by Dr. A. Price Heusner who advised section

of the temporal arteries. Accordingly, under local anesthesia with procaine hydrochloride 3 cm. vertical incisions were made over the temporal arteries successively, exposing normal auriculotemporal nerves, hard, pale, slightly pulsatile and extremely tortuous temporal arteries and swollen tortuous veins. Of each artery 1.5 to 2 cm. was isolated between ligatures and removed together with the veins and perivascular sympathetic nerves. The wounds were closed by galeal sutures alone on the left and by galeal and skin sutures on the right side. The patient experienced slight nausea and vomiting after the second side was completed. Otherwise she felt well throughout the procedure and returned to the ward in excellent condition.

Postoperatively her course was remarkable only for dramatic relief of her symptoms. There were transient swelling and redness of the left eye from the second to the fifth postoperative day. There was also some pain in the jaws, for which morphine was given on the evening of the first and second postoperative days. The headache, tenderness and swelling disappeared, and she was discharged on the seventh postoperative day, thirteen days after admission.

Follow-up Study.—When seen one month after operation she was completely free of headache and other local symptoms. She was able to carry on all of her normal activities without discomfort. She still had an occasional low grade rise in temperature in the afternoon. She had not regained her normal appetite though she had gained 1 pound (0.5 Kg.) in weight. There had been no further symptoms or signs referable to the eyes. Her legs felt somewhat stiff but she attributed this to enforced rest in bed. A few days before examination she had herpes labialis and aphthous stomatitis, which were almost healed. The radicles of the sectioned temporal arteries were still nodular and firm but were not tender. The overlying skin was still slightly discolored. Neurologic and ophthalmologic examinations gave entirely normal results. Visual acuity was 20/200 in both eyes without glasses, corrected to 20/20 on the right and 20/30 on the left with glasses.

Two and a half months postoperatively and five and a half months after onset of her disease she was again seen. The fever had subsided and there had been a marked improvement in her appetite and a general feeling of well-being. She last noted fever on October 15 and had felt well since that time, making the total duration of her disease five months. The temporal artery radicles were not tender and were less nodular. Vision and optic fundi were normal. The remainder of the examination gave unchanged results. She was considered fully recovered.

Pathologic Examination of Biopsy Specimens of Temporal Vessels.—Sections of vessels fixed in formaldehyde were stained with hematoxylin and eosin and with Verhoeff's elastic tissue stain. Multiple sections taken at various levels of the 2 cm. sections of the temporal vessels revealed a variety of pathologic changes. Most of the sections (fig. 1) revealed one or two large arteries with their venae comites and periarterial nerves bound together in a moderately dense granulomatous tissue. Scattered throughout this dense stroma are numerous small arteries, veins and nerves surrounded by a moderately dense infiltration of inflammatory cells. The density of this infiltrate varies considerably in different areas. There are many lymphocytes present and they predominate in the cellular reaction. In some places they are congregated in small foci. Occasionally they form cuffs about some of the small vessels. In most regions they are diffusely scattered throughout the stroma. Fibroblasts, histiocytes, epithelioid cells, eosinophils and occasional multinucleated giant cells are all scattered throughout the granulomatous tissue. Many of the multinucleated giant cells have a high ratio of nucleus to cytoplasm (figs. 2, 3, 4, and 5). Some of them contain as many as 30 nuclei (fig. 4).

Scattered throughout the granulomatous stroma are many small capillaries. Where these capillaries are most abundant there is considerable hemorrhage into

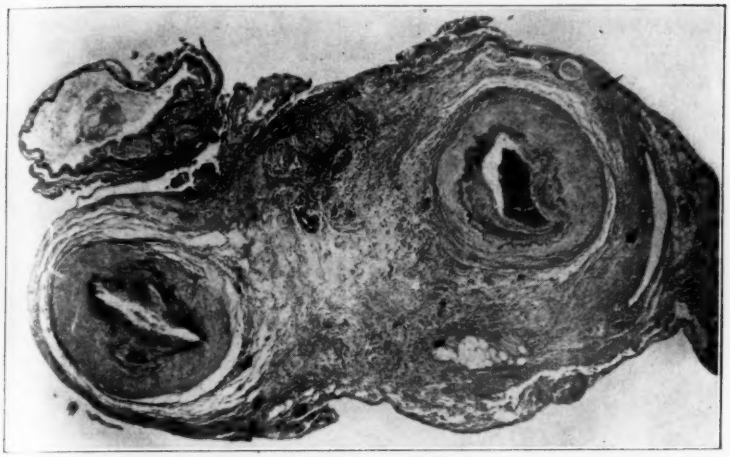

Fig. 1 (case 2).—Right temporal artery and venae comites (Verhoeff's elastic tissue stain, counterstained with Van Gieson's connective tissue stain). The arteries and veins are bound together by dense granulomatous tissues. There is reduplication of the internal elastic lamina of the arteries. The intima is thickened. There is a thrombus in the lumen of one artery. Note the eccentric thickening of the vein at the upper left side. The phlebitis involves that portion of the vein which lies adjacent to the periarterial granulomatous process. The detailed structure of this vein is shown in figure 9.

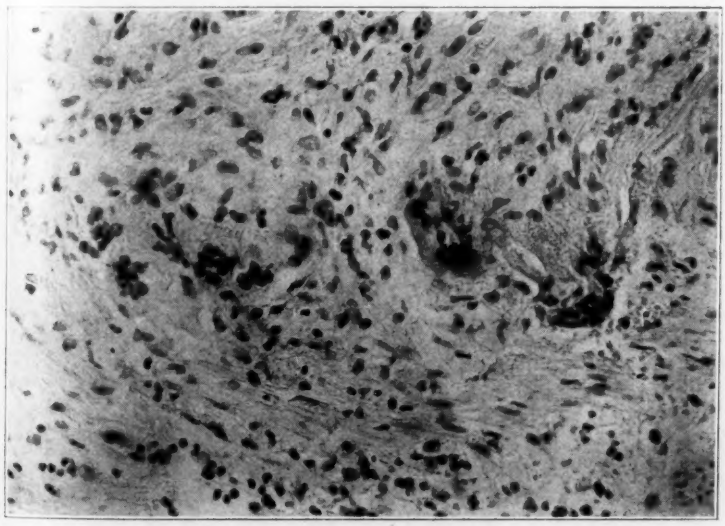

Fig. 2 (case 2).—Left temporal artery (hematoxylin and eosin stain); granulomatous reaction showing irregular distribution of epithelioid cells, lymphocytes, fibroblasts and multinucleated giant cells with irregular contours, vacuoles and apparent fusion of giant cells.

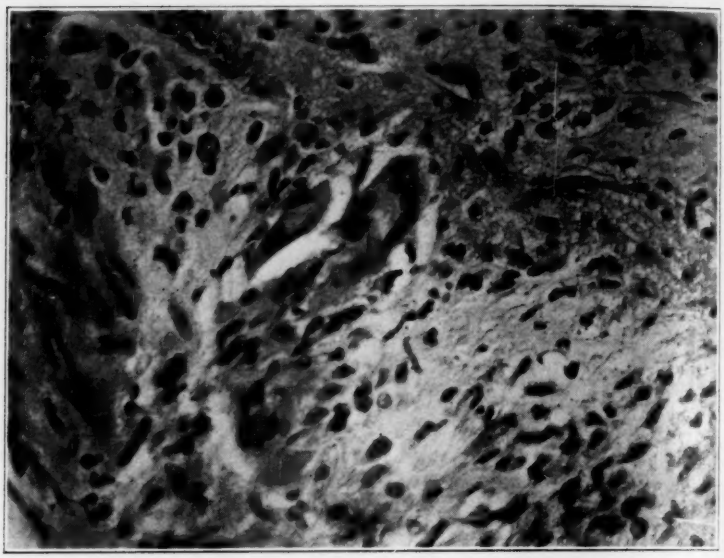

Fig. 3 (case 2).—Right temporal artery (hematoxylin and eosin stain); granulomatous reaction composed of fibroblasts, epithelioid cells and mononuclear cells. Note multinucleated giant cells with irregular contours and peripheral distribution of nuclei.

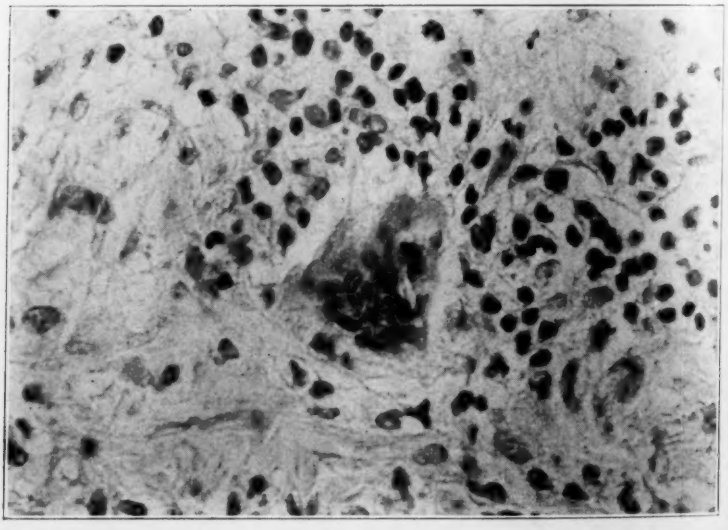

Fig. 4 (case 2).—Left temporal artery (hematoxylin and eosin stain); large multinucleated giant cell containing over 30 nuclei, lying adjacent to the internal elastic lamina and surrounded by mononuclear cells.

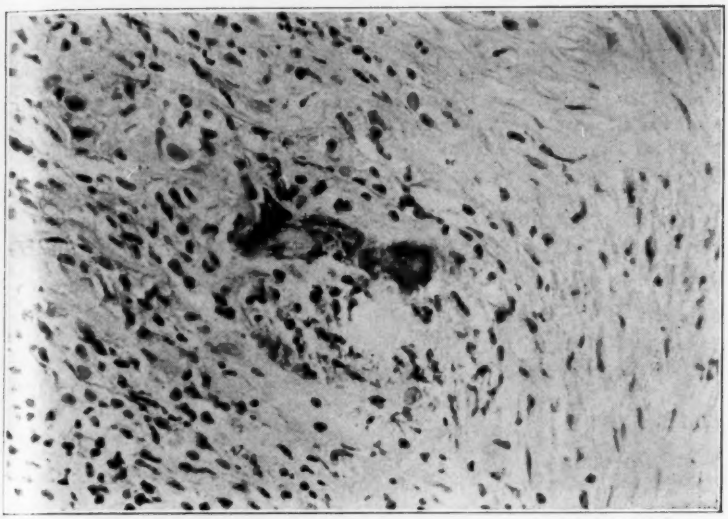

Fig. 5 (case 2).—Left temporal artery (hematoxylin and eosin stain); foreign body giant cell reacting to degenerating elastica.

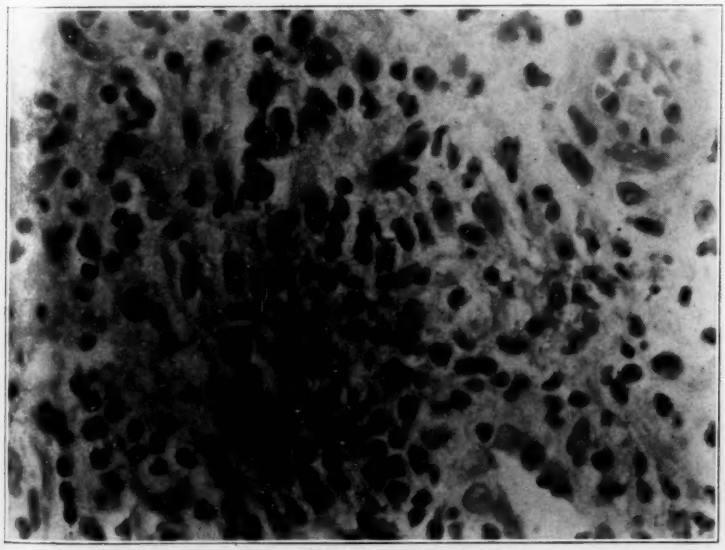

Fig. 6 (case 2).—Left temporal artery (hematoxylin and eosin stain); granulomatous nodule in media. Note the hyalinization of the nutrient vessel at upper right side. Mononuclear cells predominate throughout the lesion.

the surrounding tissue. The endothelial cells lining these capillaries are moderately swollen and in some there is a double layer of cells. Occasional mitotic figures in these endothelial cells are evidence of active proliferation. Numerous polymorphonuclear leukocytes and eosinophils are found in the lumens of the vasa vasorum. Some of these vessels show a loss in the continuity of the endothelial lining and a concomitant infiltration of polymorphonuclear leukocytes in the walls. Some of them have thickened hyalinized walls (fig. 6). The lumens of some contain hyaline thrombi. An occasional dilated lymphatic vessel is observed. Scattered throughout the granulomatous stroma are numerous small sharply circumscribed nodules usually showing some necrosis and containing lymphocytes, histiocytes, occasional eosinophils, an occasional polymorphonuclear leukocyte and a few scattered cells

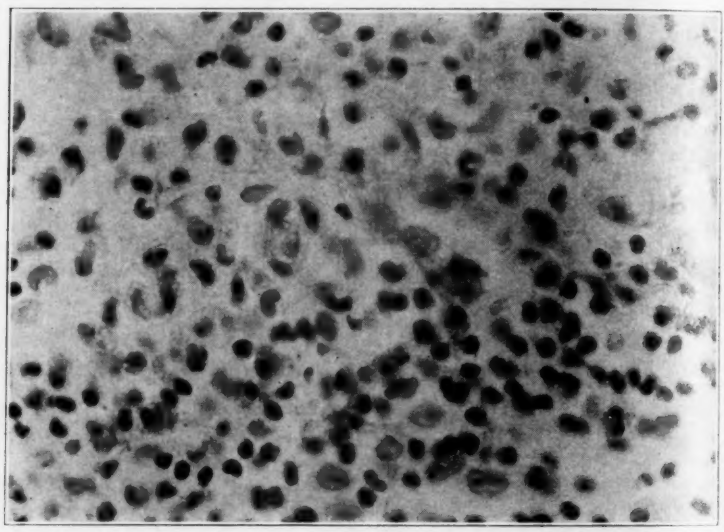

Fig. 7 (case 2).—Left temporal artery (hematoxylin and eosin stain); portion of granulomatous reaction showing numerous eosinophils. Note the granules in the cytoplasm of the eosinophils. The small deeply staining cells are lymphocytes.

undergoing karyorrhexis (figs. 6 and 7). None of these nodules have the architectural pattern of tubercles.

In those sections where the inflammatory reaction is least marked there appears to be a fairly sharp demarcation between the granulomatous tissue and the adventitia of the large arteries and veins (fig. 8). Where the inflammatory reaction is most marked the granulomatous tissue appears to replace the adventitia and, in some areas, to replace a large part of the vessel wall. This is particularly true of the veins which lie adjacent to an active focus. Here the wall of the vein adjacent to the artery is at times almost completely replaced by granulomatous tissue while the opposite wall remains intact (fig. 1). In some of the involved veins the muscularis and intima contain numerous small vessels distended with erythrocytes. There are numerous small scattered areas of hemorrhage. In some of the veins

hyalinized vasa vasorum penetrate the intima (fig. 9). In several of the veins there is an eccentric thickening of the intima with an infiltration of lymphocytes, histiocytes, epithelioid cells and occasional polymorphonuclear leukocytes. The endothelial lining is disrupted in some areas and organizing thrombi are attached to the intima.

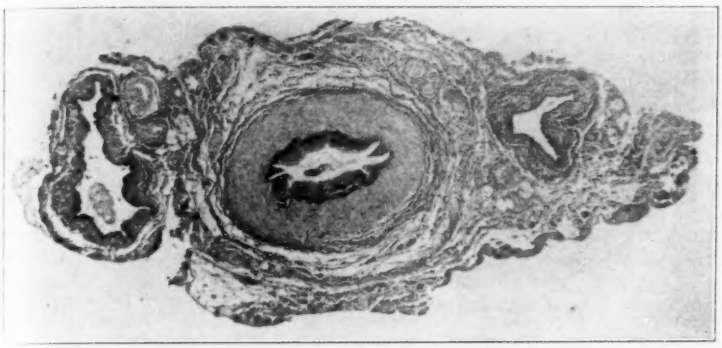

Fig. 8 (case 2).—Right temporal artery and venae comites (Verhoeff and Van Gieson stain); relatively healthy segment of artery with little evidence of granulomatous process, some reduplication of internal elastic lamina and slight intimal thickening. Venae comites are well preserved.

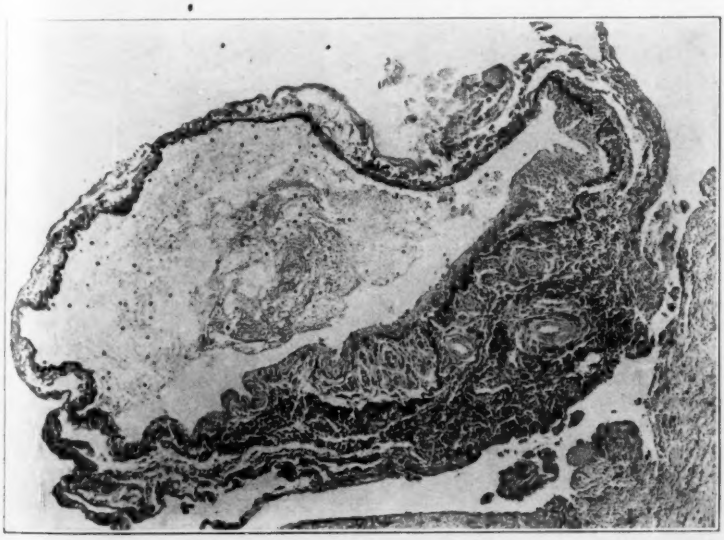

Fig. 9 (case 2).—Right temporal vein (Verhoeff and Van Gieson stain); high power enlargemen. of vein shown in figure 1. Note the granulomatous reaction adjacent to the periarterial structures. The vasa vasorum are numerous and hypertrophied and penetrate the thickened intima. The opposite wall remains intact.

In some sections of the larger arteries the muscularis is essentially unaltered (fig. 8). In other sections there are sharply circumscribed granulomatous nodules replacing either a portion of, or the entire thickness of, the media (fig. 10). These nodules are similar to those described in the periadventitial tissues. They contain areas of necrosis, lymphocytes, histiocytes, epithelioid cells and occasional eosinophils and polymorphonuclear leukocytes. In one of these nodules there are numerous multinucleated giant cells. In some sections the media of the artery is partially replaced by pale acellular collagenous tissue which is surrounded by a variety of inflammatory cells (fig. 11). The media shows a focus of arteritis at the site of origin of smaller branches (fig. 12).

In most of the arteries the internal elastic lamina is badly damaged (figs. 1, 10, 12, 13 and 14). There is marked fragmentation of the elastica and reduplication is

Fig. 10 (case 2).—Right temporal artery (Verhoeff and Van Gieson stain). This section of artery is diffusely involved by the granulomatous process. At the upper right side the muscularis is thin and necrotic. The elastica is partially destroyed. This represents a potential site for the development of an aneurysm. The lumen is almost occluded by thrombus.

frequently seen. In the area of the most intense inflammatory reaction the elastic lamina is missing (fig. 10). In many areas the elastic fibers are swollen, with the formation of sharply defined basophilic deposits resembling calcium (figs. 5, 8 and 14). Multinucleated giant cells are numerous in these areas. In most of the sections there is a fairly marked intimal thickening (figs. 10, 13 and 14). Where the muscularis is least involved the thickened intima consists of moderately dense collagenous tissue and the endothelial lining appears intact (fig. 8). Where the media is extensively involved by the granulomatous process the intima is diffusely infiltrated with inflammatory cells (fig. 10). In these areas the endothelial lining is frequently disrupted and organized thrombi are attached to the intima.

Sections of the left temporal artery reveal extensive granulomatous involvement of the media at one level. There is a loss of continuity of the muscle fibers and

the internal elastic lamina is missing in this region. An aneurysmal outpocketing extends out into the periadventitial granulomatous tissue (fig. 13). There is scattered hemorrhage in the surrounding vessel wall. Sections of the right temporal

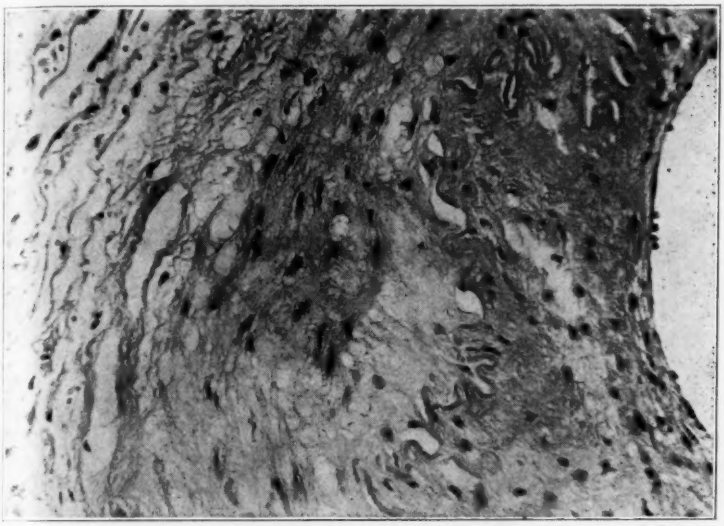

Fig. 11 (case 2).—Right temporal artery (hematoxylin and eosin stain). Pale acellular collagenous tissue external to internal elastic lamina represents medial necrosis with minimal cellular response.

Fig. 12 (case 2).—Left temporal artery (Verhoeff and Van Gieson stain). Accentuation of granulomatous process at the site of bifurcation of the artery.

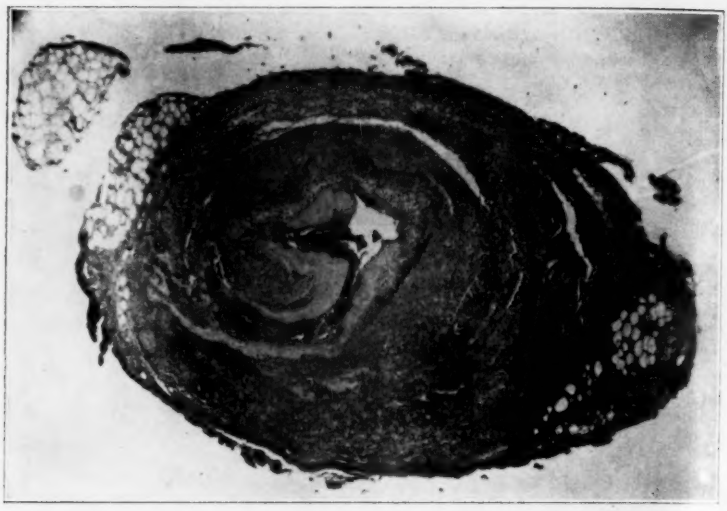

Fig. 13 (case 2).—Left temporal artery (Verhoeff and Van Gieson stain); a dissecting aneurysm which penetrates the adventitia of the artery. Note the great inflammatory reaction at this level. There are several "weak spots" in the media.

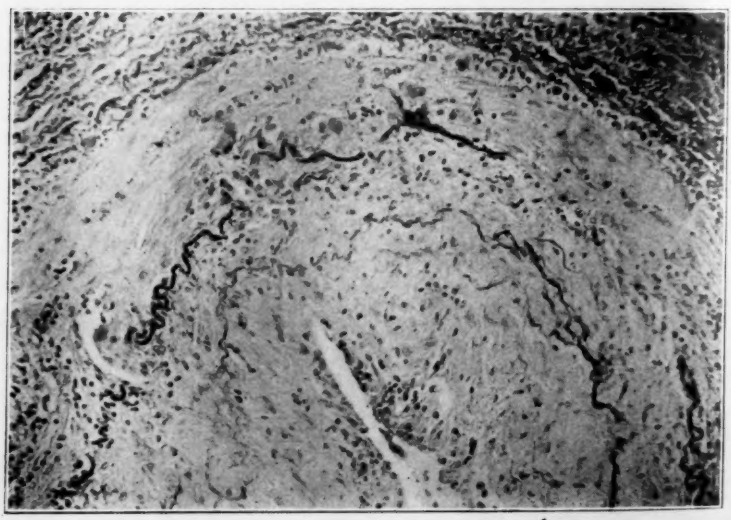

Fig. 14 (case 2).—Left temporal artery (Verhoeff and Van Gieson stain). The intima is markedly thickened. The lumen is almost obliterated. Numerous multinucleated giant cells are found external to the fragmented elastica. The media reveals necrosis with minimal cellular reaction.

artery reveal a similar destruction of the media and elastica with less marked outpocketings from the lumen (fig. 10). No deposition of hemosiderin or phagocytosis of erythrocytes is found in any of the sections.

CASE 3[8].—J. McC., a 79 year old man, was admitted to the hospital on March 5, 1947 because of headaches. He had been well except for "prostatism" relieved by perineal prostatectomy about a year prior to admission. Ten weeks before admission there rather suddenly developed a severe, throbbing, and constant bitemporal headache. His scalp was so tender that he could not comb his hair. Five weeks before admission he noticed occasional blurring of vision and ten days before admission he had diplopia. Shortly after admission he became completely blind in the right eye.

Examination revealed tortuous, swollen, tender and red temporal arteries bilaterally with discoloration and induration of the overlying skin. Ophthalmoscopic examination revealed a normal condition on the left. On the right both arteries and veins were narrow; there was a large flame-shaped hemorrhage over the disk; the retina showed numerous petechiae and some diffuse edema. The remainder of the examination gave essentially normal results.

Laboratory study revealed: hemoglobin, 54 per cent, 3,250,000 red blood cells per cubic millimeter and 10,400 white blood cells, with a normal differential count. There were 2 per cent eosinophils. The erythrocyte sedimentation rate (Westergren) was 115 mm. per hour. The urine showed albumin (1+), 5 to 10 red cells and 10 to 15 white cells per high power field in the sediment. The spinal fluid was under normal pressure and chemically and serologically normal, with 28 mg. protein per hundred cubic centimeters.

During his stay in the hospital he had a low grade fever. A biopsy specimen of the temporal artery on the right was taken with the patient under local anesthesia and caused relief of the headache almost immediately. The low grade fever and blindness persisted.

Pathologic study of the biopsy specimen of the temporal artery revealed active arteritis characterized by scarring of the adventitia, active chronic granulomatous inflammation of the media with the development of multinucleated giant cells, and obliterative endarteritis in which there was mucoid intercellular deposit. The pathologic diagnosis was "temporal arteritis."

CASE 4.—A. S., a 67 year old housewife was admitted to the hospital on March 8, 1947 because of headache and blindness. She had been well until November 1946 when general weakness led to study of the blood. Anemia, which was not further clarified, was found and intramuscular injection of liver extract was said to have corrected the weakness and the anemia. In December 1946 severe and constant headache developed rather suddenly over the vertex. This soon shifted to a severe, throbbing, constant bitemporal ache. Fever with a temperature of 101 F. was noted. Two weeks before admission she noticed a "smoke screen" before the right eye and became blind in that eye. She was totally blind in this eye for a week and then vision improved to the point where she could distinguish objects grossly.

Examination revealed tortuous, swollen, red and tender temporal arteries bilaterally with discoloration and slight induration of the overlying skin. Ophthalmoscopic examination of the left eye gave normal results for her age. The right optic disk was pale and there was some edema of the retina, but no hemorrhages were seen. The remainder of the examination gave essentially normal results.

Laboratory study revealed: hemoglobin, 60 per cent, 3,150,000 red blood cells per cubic millimeter and 9,700 white blood cells, with a normal differential count. Eosinophils were not seen. Routine urinalysis gave entirely normal results. The

8. Dr. Sigfried Thannhauser permitted us to report this case.

erythrocyte sedimentation rate (Westergren) was 132 mm. per hour. Roentgenograms of the chest, skull and gastrointestinal tract showed them to be normal.

During her stay in the hospital she had a low grade fever. Those observing her felt that there was definite improvement in the vision of her right eye even during a short period of observation. Her headache was not excessively severe, and she was discharged on symptomatic therapy.

CASE 5.—E. H., a 75 year old widow, was admitted to the hospital on March 25, 1947 because of headaches. She had been well until two months prior to admission, when severe, constant, throbbing bitemporal headache developed. She had tenderness of the scalp with some swelling in the temporal regions and of the left ear. The swelling had subsided but the headache persisted, especially on the left. There were no visual symptoms.

Examination revealed a swollen, tortuous and tender left temporal artery. On the right the temporal artery was hard, "stringlike," and without pulsation. There were slight induration and discoloration of the overlying skin. Ophthalmoscopic data were normal for her age. The remainder of the examination gave normal results.

Laboratory study revealed: hemoglobin, 78 per cent, 4,310,000 red blood cells per cubic millimeter and 10,000 white blood cells, with a normal differential count. There was 1 per cent of eosinophils. The erythrocyte sedimentation rate (Westergren) was 37 mm. per hour. Routine urinalysis gave entirely normal results. Roentgenograms of the skull showed slight hyperostosis frontalis interna.

It was thought that her disease was subsiding spontaneously. She was therefore discharged on symptomatic therapy.

SUMMARY OF THE REPORTED CASES

The five cases reported seem to fulfil the essential criteria of the disease entity temporal arteritis. Four of the patients were women and all were within the age range of previously reported cases. The typical systemic symptoms of fever, malaise, anorexia, loss of weight and weakness were present in all. All showed tenderness, swelling, redness and nodularity of the temporal arteries bilaterally. In case 1 the rapid erythrocyte sedimentation rate, the great and sustained loss of weight, and the microscopic hematuria suggested the possibility of diffuse arterial disease. The patient recovered, however, and is now—twelve months after the onset of the disease—reasonably well. She has had persistent blindness which seems to be improving slightly. She has failed to regain weight but does not eat well because of the loss of zest for food incident to loss of vision. Her condition at present would seem to rule out active generalized arterial disease.

Case 2 seemed to follow a typical course, including the dramatic relief of headache and local symptoms afforded by section of the temporal arteries. Systemic symptoms persisted for about two months postoperatively and then subsided. This probably represents simply the normal course of the disease, only the local symptoms being benefited by operation. Transient unilateral blindness occurred in this case before operation but disappeared in a few hours without therapy. Examination

of the biopsied vessels revealed the occurrence of secondary phlebitis and arterial aneurysm; the latter has not been described previously as present in temporal arteritis.

Case 3 is typical and also demonstrates the relief of local symptomatology which biopsy affords. Case 4 is of particular interest in that there was complete blindness in one eye for a week with unusually complete return of vision in that eye. As a rule blindness of more than a few hours' duration in this disease has been permanent. Case 5 demonstrates a mild but typical case of temporal arteritis with the disease apparently confined to the temporal arteries.

The essential data of all the cases reported to date have been summarized in table 1. This includes the 43 cases found in the literature and our 5 cases. Analysis of the data thus presented reveals the definite uniformity of the clinical features of the disease. These clinical features are presented for the sake of brevity in table 2.

The essential data concerning 9 other cases similar to, and in some cases, perhaps identical with, temporal arteritis are presented in table 3. These cases have been excluded from the temporal arteritis group. The case reported by Paviot, Chevallier, Guichard and Damez[9] was clinically indistinguishable from temporal arteritis. A mitral heart murmur was found during the course of the disease and the patient was treated effectively with salicylates, which led the authors to believe that all his symptoms were rheumatic manifestations. Biopsy was not done, and this case has been excluded only because of insufficient data. Similarly Chavany's[10] case was, from the data given, indistinguishable from temporal arteritis, and he implied that other cases had been seen. The data were inconclusive, however, and the case was therefore excluded. Barnard[11] has reported a case with autopsy observations consisting of arteritis of the coronary, cerebral and retinal arteries, which was histologically similar to that of temporal arteritis. Although tubercle bacilli were not demonstrated, Barnard believed the disease to be tuberculous arteritis. Headache and "erysipelas of the face" were mentioned clinically but pathologic data on the temporal arteries were not given, and hence this case has been excluded. The mesaortitis described in the cases of Sproul and Hawthorne[12] and the "giant cell arteritis" described by Gilmour[13] have been referred to as being similar to temporal arteritis[13a]

9. Paviot, J.; Chevallier, R.; Guichard, A., and Damez, M.: Lyon med. **154**:45-51 (July 15) 1934.

10. Chavany, J. A.: Presse méd. **44**:347-348 (Feb. 29) 1936.

11. Barnard, W. G.: J. Path. & Bact. **40**:433-436 (May) 1935.

12. Sproul, E. E., and Hawthorne, J. J.: Am. J. Path. **13**:311-323 (March) 1937.

13. Gilmour, J. R.: J. Path. & Bact. **53**:263-267 (Sept.) 1941.

13a. Cooke and others.[2] Chasnoff and Vorzimer.[3]

TABLE 1.—*Essential Data on All the Reported Cases of Temporal Arteritis*

No.	Author and Date	Place	Sex and Age	Arteries Affected	First Symptom	Systemic Symptoms	Duration	Treatment	Outcome	Culture
1	Horton, Magath and Brown, 1932 (1)	Minn., U. S.	F, 55	Temporal	Fever, malaise, anorexia	Fever, weakness, malaise, loss of weight	4-6 mo.	Biopsy	Recovered	Actinomyces
2	Horton, Magath and Brown (1)	Neb., U. S.	M, 68	Temporal	Pain in jaws	Usual, also dental sepsis	4-6 mo.	Biopsy	Recovered	Actinomyces
3	McDonald and Moser, 1937 (1)	Ind., U. S.	F, 60	Temporal	Headache	Usual	5 mo.	Lextron, salicylates	Recovered	Staph. aureus
4	Artucio, Munoz and Falcon, 1937 (*)	Uruguay	M, 57	Right temporal	Not stated	Uusual, also hypertension	2 mo.	None	Recovered	None
5	Horton and Magath, 1937 (4)	Wis., U. S.	F, 69	Temporal	Systemic	Usual	4-6 mo.	Iodides, acetylsalicylic acid, biopsy	Recovered	Neg.
6	Horton and Magath, 1937 (4)	Wis., U. S.	F, 75	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
7	Horton and Magath, 1937 (4)	Iowa, U. S.	M, 72	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
8	Horton and Magath, 1937 (4)	Ore., U. S.	M, 65	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
9	Horton and Magath, 1937 (4)	Minn., U. S.	F, 68	Temporal	Systemic	Usual	4-6 mo.	Biopsy, acetylsalicylic acid, iodides	Recovered	Neg.
10	Jennings, 1938 (23)	England	F, 66	Temporal, retinal, (?) radial and foot	Systemic and headache	Usual, pain in limbs	18 mo.	Biopsy	Blind Well	None
11	Jennings, 1938 (23)	England	F, 72	Temporal	Systemic	Usual	Some wks. each side	None	Recovered	None
12	Bain, 1938 (32)	England	F, 71	Temporal	Systemic and pain in neck	Usual, sore throat, disoriented	1 month	Azosulfamide	Rheumatism	None
13	Thevinaud, 1939 (33)	France	M, 66	Temporal, retinal	Blindness	Usual, lime burns to eyes	Few months	Biopsy	Recovered Blind, o. u.	None
14	Dick and Freeman, 1940 (16)	Ill., U. S.	F, 65	Temporal, retinal, left, (?) occipital	Systemic	Uusal	4 mo.	Sulfanilamid ,Biopsy	Blind, o. s.	Strep. viridans
15	Dick and Freeman, 1940 (16)	Ill., U. S.	F, 76	Temporal	Headache	Usual, d plopia weakness, pai s in joints	13 mo.	Sulfanilamide	Recovered	None

**Artucio, H.; Munoz, M., and Falcon, C. M.: Personal communication cited by Horton and Magath.[4]

†Bain, C. W. C.: Lancet 1:517 (Feb. 26) 1938.

‡Thevinaud, M.: Bull. et mém. Soc. d. chir. de Paris 31:136-137 (Feb.) 1939.

No.	Author and Date	Place	Sex and Age	Arteries Affected	Local Symptoms	Systemic Symptoms	Duration	Treatment	Outcome	Culture
16	Bowers, 1940 (15)	Wash., U. S.	F, 65	Temporal, (?)Cerebral	Headache	Usual—neurosis, hypertension	14 mo.	Vit. liver, iodides, biopsy	Recovered	Gram-cocci
17	Sprague and McKenzie, 1940 (21c)	Canada	M, 66	Both temporal	Headache	Typical	7 mo.	Biopsy	Recovered	None
18	Scott and Maxwell, 1941 (24)	Ky., U. S. A.	F, 70	Temporal and retinal	Weakness, anorexia	Typical, mild diabetic, tender arteries of arm	5 mo.	Biopsy, vit. B	Recovered Blind, O.D.	Neg.
19	Hoyt, Perera and Kauver (25)	Mass., U. S.	F, 51	Both temporal	Headache	Typical	2 mo.	Sulfanilamide, aceto-phenetidin, biopsy	Recovered	None
20	Hoyt, Perera and Kauver (25)	Mass., U. S.	F, 61	Both temporal	Pains in joints	Typical	12 mo.	Sulfanilimide, biopsy	Recovered, residual arthralgia	None
21	Hoyt, Perera and Kauver (25)	Mass., U. S.	F, 67	Both temporal	Muscle aches	Typical, asthma, hypertension	18 mo.	Biopsy	Recovered	None
22	Sproul, 1942 (29)	N. Y., U. S.	M, 68	Generalized	Headache	Typical, diabetic coronary disease	8 wk.	Supportive	Died, cardiac failure	None
23	Schaefer and Sanders, 1942 (31)	Kansas, U. S.	F, 62	Right temporal	Headache, systemic symptoms	Typical delirium	2 mo.	Sanders Oscillating Bed	Recovered	None
24	Murphy, 1942 (34)	N. Y.,	F, 71 U. S.	Both temporal	Headache, sweats	Usual, vertigo hypertension	6 mo.	Cobra venom, biopsy	Recovered	None
25	Johnson, Harley and Horton, 1943 (27)	Minn., U. S.	F, 61	Temporal and retinal	Systemic	Typical	6 mo.	None	Recovered, Blind, O.S.	None
26	Johnson, Harley and Horton, 1943 (27)	Minn., U. S.	M, 75	Temporal and retinal	Headache	Typical, coronary disease	Not stated	None	Recovered, Blind, O.U.	None
27	Johnson, Harley and Horton, 1943 (27)	Minn., U. S.	F, 76	Temporal and retinal	Systemic	Typical	Not stated	Not stated	Under observation	None
28	Chasnoff and Vorzimer, 1944 (3)	N. Y., U. S.	F, 63	Temporal, generalized	Pain, back and groins	Typical, later depression and stupor	14 mo.	Biopsy	Died	None
29	Profant, 1944 (17)	Calif., U. S.	F, 76	Right temporal	Headache	Typical, exacerbation with tooth extraction	11 mo.	Supportive	Recovered	None
30	Profant, 1944 (17)	Calif., U. S.	F, 61	Both temporal	Headache	Typical, angina and hypertension	2 mo.	Sulfathiazole	Recovered	None
31	Brown and Hampson, 1944 (35)	England	M, 61	Temporal	Rheumatic pains	Typical	6 mo.	Biopsy	Recovered	None

§Murphy, J. R.: New York State J. Med. 42:2236-2237 (Dec. 1) 1942.

No.	Author and Date	Place	Sex and Age	Arteries Affected	First Symptoms	Systemic Symptoms	Duration	Treatment	Outcome	Culture
32	Shannon and Solomon, 1945 (36)	Mass., U. S.	M, 73	Temporal and retinal	Pain in jaws	Typical	2 mo.	Biopsy	Recovered, blind, O.U.	None
33	Kilbourne and Wolff, 1946 (19)	N. Y., U. S.	M, 68	Temporal	Pain in jaws	Typical, angina pectoris	3 mo.	Biopsy	Recovered, later died of coronary thrombosis	None
34	Cooke and others, 1946 (2)	England	M, 66	Generalized	Blind, O.S.	Typical, Inter. claudication, paral. agitans	6 mo.	Biopsy	Recovering, blind, O.S., later died	None
35	Cooke and others, 1946 (2)	England	F, 66	Temporal and retinal	Systemic	Typical, scalp eczema	10 mo.	Sulfonamide	Recovering, blind, O.U.	None
36	Cooke and others, 1946 (2)	England	F, 69	Generalized	Pain in thigh	Typical, venous thromboses, polyneuritis	30 mo.	Biopsy	Died, blind	None
37	Cooke and others, 1946 (2)	England	M, 71	Temporal	Headache	Typical	24 mo.	Biopsy	Recovered	None
38	Cooke and others, 1946 (2)	England	M, 69	Temporal, no foot pulses	Pains in joints	Typical, inter. claudication	12 mo.	Biopsy	Recovered	None
39	Cooke and others, 1946 (2)	England	F, 73	Generalized	Systemic	Typical, later disorientation	14 mo.	Biopsy	Blind, died	None
40	Cooke and others, 1946 (2)	England	F, 68	Temporal	Headache, pains in legs	Typical	12 mo.	Biopsy, nicotinic acid	Recovering	None
41	Dantes, 1946 (22)	N. Y., U. S.	F, 55	Temporal (?) rt. dorsalis pedis	Headache	Typical	12 mo.	Biopsy	Recovered	None
42	Gordon and Thurber 1946 (26b)	N. Y., U. S.	M, 65	Temporal	Pain in thighs	Typical	4 mo.	Biopsy	Recovered	None
43	Curtis, 1946 (26d)	Utah, U. S.	F, 71	Temporal, retinal, (?) cerebral	Headache, vertigo	Typical	3½ mo.	Biopsy	Blind, O.U., died	Neg.
44	Crosby and Wadsworth	Maine, U. S.	F, 73	Temporal and retinal	Headache	Typical	3 mo.	Amyl nitrate, nicotinic acid	Recovered, blind, O.U.	None
45	Crosby and Wadsworth	Maine, U. S.	F, 64	Temporal	Headache	Typical	5 mo.	Biopsy	Recovered	None
46	Crosby and Wadsworth	R. I., U. S.	M, 79	Temporal and retinal	Headache	Typical		Biopsy	Recovering, Blind, O.D.	None
47	Crosby and Wadsworth	Mass., U. S.	F, 67	Temporal and retinal	Weakness	Typical		None	Recovered, Blind, O.D.	None
48	Crosby and Wadsworth	Mass., U. S.	F, 75	Temporal	Headache	Typical		None	Recovering	None

| No. | Author and Date | Place | Sex and Age | Arteries Affected | First Symptoms | Systemic Symptoms | Duration | Treatment | Outcome | Culture |

**Shannon, E. W., and Solomon, J.: Bilateral Temporal Arteritis with Complete Loss of Vision, J. A. M. A. 127:647-649 (March 17) 1945.

TABLE 2.—*Clinical Features of Temporal Arteritis (From the Forty-Eight Reported Cases)*

Distribution: England, France, Canada, Uruguay, United States.
Age: 55 to 79 years. Average: 67.4 years.
Sex: Females: 32 cases. Males: 16 cases. Female/Male ratio: 2/1.
Initial symptoms: Local: 25 (5)*, systemic: 26 (5)*, blindness: 2.
Local symptoms: Headache, pain in adjacent structures, blindness, tender, red nodular temporal arteries, local edema.
Systemic symptoms: Malaise, anorexia, fever, loss of weight, weakness.
Arteries involved: Temporal 48, retinal 16, generalized 5, (?) cerebral, occipital, radial, dorsalis pedis.
Duration: Two to thirty months; average: 7¾ months.
Treatment: Salicylates, sulfonamide compounds, arsenic, mercury, iodides, vitamins, liver extract, cobra venom, section of arteries.
Culture: Actinomyces, Staphylococcus aurens, Streptococcus viridans; many not done; most were sterile.
Outcome: Four died of other causes, 5 of the disease; 6 deaths attributed to the disease; mortality 12.5%.

*Five patients had both local and systemic symptoms initially.

TABLE 3—*Essential Data on Cases Similar to but Excluded from Temporal Arteritis*

No.	Author—Date	Place	Sex and Age	Arteries Affected	First Symptom	Systemic Symptoms	Duration	Treatment	Outcome	Culture
1	Paviot and others, 1934 (9)	France	M, 61	Temporal	Systemic	Fever, pallor, anorexia and mitral-regurgitation	3 mo.	Arsenic, mercury, Salicylates	Recovered	None
2	Barnard, 1933 (11)	England	F, 62	Coronary, cerebral, Retinal	Headache	Blind in one eye, weakness, "erysipelas of face"	10 wk.	None	Died	Neg.
3	Chavany, 1936 (10)	France	F, 63	Temporal	Headache	Fever, loss of weight, rheumatism	Not stated	Not stated	Recovered	None
4	Sproul and Hawthorne, 1937 (12)	N. Y., U.S.	M, 76	Aorta, iliac	Prostatism	None	Prostatism, 3 yr.	Prostatectomy	Died of Pneumonia	None
5	Sproul and Hawthorne, 1937 (12)	N. Y., U. S.	M, 50	Aorta, iliac, carotid	Precordial pain	Congestive heart failure	1 year	Supportive	Died of heart failure	None
6	Gilmour, 1941 (13)	England	F, 23	Aorta and branches of aorta arch	Giddiness, sweats	Neuritis, congestive heart failure, hemoptysis	6 mo.	Supportive	Died	None
7	Gilmour, 1941 (13)	England	F, 59	Aorta, carotid and branches	"Influenza"	Influenza, measley rash, peeling hands and feet, hemiplegia and coma	5 mo.	Supportive	Died	None
8	Gilmour, 1941 (13)	England	M, 63	Aorta, carotids and branches	"Influenza"	Influenza, headache, failing vision, mental dulness	9 mo.	Supportive	Died of "stroke"	None
9	Gilmour, 1941 (13)	England	F, 64	Aorta and major branches	"Influenza"	Influenza, cardiac, abdominal aneurysm enteritis, congestive heart failure	26 mo.	Supportive	Recovering	None

without involvement of the temporal arteries. There are also differences in age group, symptomatology and pathology which justify the exclusion of these cases from the temporal arteritis group.

COMMENT

In the fifteen years since Horton, Magath and Brown[1] first described "arteritis of the temporal arteries" as a disease entity 43 cases which seem to warrant this designation have been reported (table 1). Many other cases have undoubtedly been recognized and not reported, yet the disease is relatively rare. Critical analysis of the cases reported to date has establishel certain facts about the disease. The constancy with which the major clinical features have been found is striking. With the exceptions of the occurrence of blindness and a definite though small mortality, the general clinical picture corresponds closely to the original description of the disease. The symptoms may be conveniently divided into local and systemic. Local symptoms have consisted of severe, throbbing headache with swollen, tender, nodular and thrombosed temporal arteries and pain in the adjacent structures such as the scalp, face, jaws, eyes and temporomandibular joints. Systemic symptoms of fever, malaise, weakness, anorexia and loss of weight have appeared almost constantly. The initial complaints were about equally divided between local and systemic; 26 patients presented themselves with systemic symptoms and 25 with headache; 5 had both local and systemic symptoms. In 2 cases blindness was the presenting complaint. Local signs of inflammation of the temporal arteries frequently postdated the pain by a few days to several weeks. Systemic symptoms have occurred a few weeks or even a few months before the local signs became apparent. Thus prolonged observation may be required in order to ascertain the diagnosis. Once the characteristic changes in the temporal arteries have developed, the diagnosis is obvious and other conditions need not be seriously considered in the clinical differential diagnosis. The duration of the disease has varied from eight weeks to thirty months. The average duration for the reported cases was seven and three-quarters months.

The etiology of temporal arteritis, as of most other forms of arteritis, remains unknown. Horton and his co-workers [1] found actinomyces from culture of the biopsy specimens of the first 2 cases but concluded after study that this was probably a contaminant. McDonald and Moser[14] found Staphylococcus aureus, Bowers[15] found "gram-positive cocci in

14. MacDonald, J. A., and Moser, R. H.: Ann. Int. Med. **10**:1721-1726 (May) 1937.

15. Bowers, J. M.: Arteritis of the Temporal Vessels: Report of a Case, Arch. Int. Med. **66**:384-392 (Aug.) 1940.

16. Dick, G. F., and Freeman, G.: Temporal Arteritis, J.A.M.A. **114**:645-647 (Feb. 24) 1940.

clusters," and Dick and Freeman [16] found Streptococcus viridans. No organism has been found consistently or in a significant number of cases. Cultures of the biopsy specimens of the artery segments have not been taken in most cases. There is no clinical evidence to indicate that allergy is a factor in the etiology and no case in which there was significant eosinophilia in the peripheral blood has been reported. Of the 43 reported cases hypertension was present in 5, coronary heart disease in 4, diabetes in 2, asthma, intermittent claudication, paralysis agitans, eczema of the scalp, and polyneuritis each in 1 case. Oral sepsis has been emphasized in 3 cases, and in most reports the status of the teeth is not mentioned. In Profant's [17] case 1 there was a definite exacerbation of symptoms after extraction of an infected tooth. The disease has occurred in edentulous patients, however, so that the possibility of oral sepsis per se being the etiologic factor seems remote. Distant foci of infection including oral sepsis, with or without bacterial allergy, have been hypothesized as being etiologically significant.[18] As yet the hypothesis is unproved. The fact

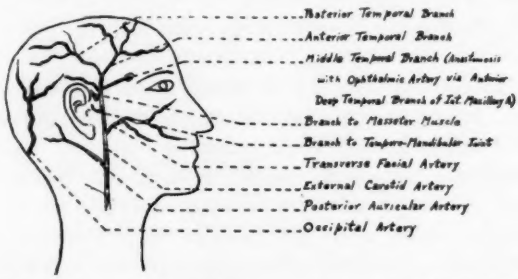

Fig. 15.—Schematic diagram of the temporal artery and its branches.

that this disease occurs apparently only in the older age group, of 55 to 79 years, would suggest that degenerative arterial disease is at least associated with it and perhaps predisposes to it. Trauma to the temporal arteries, predisposed by their superficial location and marked tortuosity, may possibly be a factor in the pathogenesis of the lesion.

Laboratory findings in the disease are quite constant but not diagnostic. There is usually a mild anemia and a mild to moderate leukocytosis with a preponderance of polymorphonuclear leukocytes and some "shift to the left." The sedimentation rate is usually moderately increased and may be extremely rapid.

The inflammatory process in the temporal arteries is the characteristic and dominant feature of the disease. Evidence of arteritis of other branches of the external carotid artery has been stressed by some authors,

17. Profant, H. J.: Ann. Otol., Rhin. & Laryng. **53**:308-325 (June) 1944.
18. Curtis, H. C.: Am. J. Med. **1**:437-446 (Oct.) 1946.

notably Kilbourne and Wolff.[19] The clinical symptomatology suggested that other cranial vessels were involved. Careful study of the anatomic distribution of the temporal arteries (fig. 15) shows that this is not necessarily true. The first branch of the temporal artery is the transverse facial artery, which if involved would explain the pain over the face. Two small branches then go to the masseter muscle and the temporomandibular joint, thus explaining the difficult mastication and pain in the jaws and temporomandibular joints. Pain and redness around the eyes and over the forehead and scalp may be accounted for by the involvement of the anterior temporal branches and their tributaries. Similar symptoms over the parietal and occipital regions may be attributed to the posterior branches and their tributaries. Phlebitis probably contributes to local edema for, although it has been denied by most investigators, phlebitis has been found by some[20] and was demonstrated in our case 2. Arteritis of the occipital artery has been assumed by some[21] but never proved. In 1 case [2] biopsy was attempted but diseased vessels could not be demonstrated. The symptomatology suggesting such involvement may have been due to arteritis of the smaller radicles of the posterior temporal branch.

Definite evidence of arteritis in vessels other than the branches of the temporal artery in cases not autopsied is sparse despite general agreement that there must be some generalized arteritis. Lack of pulsation in the dorsalis pedis and posterior tibial arteries has been pointed out but is of a questionable significance in this age group. Dantes[22] noted an area of thickening on the right dorsalis pedis artery in his case. Tenderness was not mentioned and biopsy could not be performed. The question of radial artery involvement was raised in Jenning's[23] case 1, and Scott and Maxwell[24] mentioned tenderness along the course of the arteries of the arm. In case 6 of Cooke and his associates[2] a radial arteritis was actually found at autopsy. The presence of pains in the joints and muscles and generalized pain in the limbs has been offered as evidence of brachial and femoral arteritis, but this has not been confirmed. Residual arthralgia was noted in 1 case.[25] Coronary and mesenteric

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19. Kilbourne, E.D., and Wolff, H. G.: Ann. Int. Med. **24**:1-10 (Jan.) 1946.

20. Chasnoff and Vorzimer.[8] Heusner.[8a]

21. (*a*) Chasnoff and Vorzimer.[8] (*b*) Bowers.[18] (*c*) Sprague, P. H., and MacKenzie, W. C.: Canad. M. A. J. **43**:562-564 (Dec.) 1940.

22. Dantes, D. A.: Temporal Arteritis, J.A.M.A. **131**:1265-1269 (Aug. 17) 1946.

23. Jennings, G. H.: Lancet **1**:424-428 (Feb. 19) 1938.

24. Scott, T., and Maxwell, E. S.: Internat. Clin. **2**:220-223 (June) 1941.

25. Hoyt, L. H.; Perera, G. A., and Kauvar, A. J.: New England J. Med. **225**:283-286 (Aug. 21) 1941.

arteritis have been mentioned in the fatal cases; yet in no case has coronary or mesenteric thrombosis been reported in the course of the disease. Increasing angina pectoris was not noted in cases with preexisting angina.

Cerebral arteritis has been hypothesized by Bowers,[15] Chasnoff and Vorzimer[3] and others[26] but is rather difficult to evaluate. The usual symptoms which led to the assumption of cerebral involvement were mental confusion, depression and lassitude which, in the face of anorexia with concomitant deficiencies, dehydration and fever, especially in the age group involved, require extremely careful evaluation. Cooke and his co-workers[2] found a spinal fluid protein of 130 mg. per hundred cubic centimeters in their case 1. In cases 2 and 4 there were significant elevation of protein (70 mg. per hundred centimeters) and in cases 5, 6 and 7 values were normal. In our cases 1 and 3 values were normal for the spinal fluid protein. In cases 3 and 6 of Cooke and his associates,[2] with a high spinal fluid protein in one and with a normal spinal fluid protein in the other, there was definte cerebral arteritis at autopsy. It is also interesting to note that of the 6 patients who died of or during the disease, 4 died of cerebral vascular accidents.

Disease of the retinal vessels in temporal arteritis is common and is the most formidable complication seen in the nonfatal case. Blindness was found in 13 of the 43 previously reported cases and in 3 of our cases, a total incidence of 16 of 48 cases, or 33.3 per cent. In 9 of these cases blindness was bilateral and in 7, unilateral. In a few cases gross perception of light has returned, as in our case 1. Transient amaurosis for a few hours has also been noted and was exemplified in our case 2. This is presumably due to spasm of the retinal vessels. Blindness lasting for a week and subsequently subsiding was found in our case 4. This is unusual, and no good explanation is apparent. Perhaps vasospasm of longer duration led to ischemia and edema of the retina producing blindness until the edema subsided and permitted return of function to those nerve fibers not irreversibly damaged. Other ocular symptoms such as scotomas, aching of the eyes, diplopia, pain on motion and photophobia are of fairly common occurrence. The mechanism of blindness is not well understood. Patients often complain of "spots," blind spots, or quadrantic field defects prior to loss of vision, which is usually described as "a shade being gradually drawn." Careful ophthalmoscopic findings have not been recorded in many cases. There is no proof that the process spreads from the temporal artery along vascular pathways to the artery of the

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26. (*a*) Scott and Maxwell.[24] (*b*) Gordon, L. Z., and Thurber, D. C.: Temporal Arteritis: Report of a Case and Comparison with Respect to Periarteritis Nodosa, Arch. Path. **42**:402-411 (Oct.) 1946. (*c*) Post, L. T., and Sanders, T. E.: Tr. Am. Ophth. Soc. **41**:241-250, 1943. (*d*) Curtis.[18]

retina. A possible pathway for such extension from the temporal to the retinal vessels has been pointed out by Johnson, Harley, and Horton,[27] who state that "the anterior deep temporal arteries have an anastomosis with the lacrimal branch of the ophthmalic artery" which gives off the central artery of the retina as well as the anterior and posterior branches to the optic nerve. The anterior deep temporal artery is usually a branch of the internal maxillary artery. The former does have a large anastomosis with the middle temporal branch of the temporal artery so that the pathway is complete though extremely indirect. Thus far no case of blindness in either eye has been reported without arteritis of the corresponding temporal artery. Longitudinal extension along the pathway mentioned from the temporal to the retinal arteries has not been demonstrated but this method of spread elsewhere has been suggested by postmortem findings.[2] Since blindness is usually a late manifestation of the disease, section of the middle temporal branch of the temporal artery early in the course of the disease might conceivably be of some prophylactic value against the development of blindness.

Wagener[28] has reviewed carefully and comprehensively the subject of blindness in temporal arteritis. He classifies the lesions into three groups: closures or thromboses of the central artery of the retina or of branch arterioles, ischemic optic neuritis and an indeterminate group. He also reviews the cases with blindness thus far described, classifies them and describes the ophthalmoscopic findings in each. All blindness in this disease must be attributed in the final analysis to retinal or optic nerve ischemia secondary to arteritis. The only histologic ocular findings which are available are those of case 6 of Cooke and associates,[2] who found that the "optic nerves showed marked softening" and "the lumen (of both retinal arteries) was obliterated by cellular fibrous tissue obviously formed during the organization of a thrombus" (see Cooke and associates,[2] fig. 7). No treatment or prophylactic measures for the blindness have been offered. Johnson, Harley and Horton [27] believe vasodilator drugs to be ineffective and even harmful. Our first patient became blind in spite of treatment with amyl nitrate and nicotine acid.

An evaluation of temporal arteritis as a possible pathologic entity must include the distribution of the lesions as well as the histologic variations. There are relatively few histologic lesions which are pathognomonic of a single disease process. The tissues of the body are capable of reacting to noxious stimuli in a limited number of ways. The arteries and veins are no exception to this rule. Similar histologic patterns may be produced by a wide variety of stimuli. Conversely, a variety of patterns may be

27. Johnson, R. H.; Harley, R. D., and Horton, B. T.: Am. J. Ophth. **26**:147-151 (Feb.) 1943.

28. Wagener, H. P.: Am. J. M. Sc. **212**:225-228 (Aug.) 1946.

produced by apparently identical stimuli in different persons under different circumstances. There are apt to be considerable variations in the

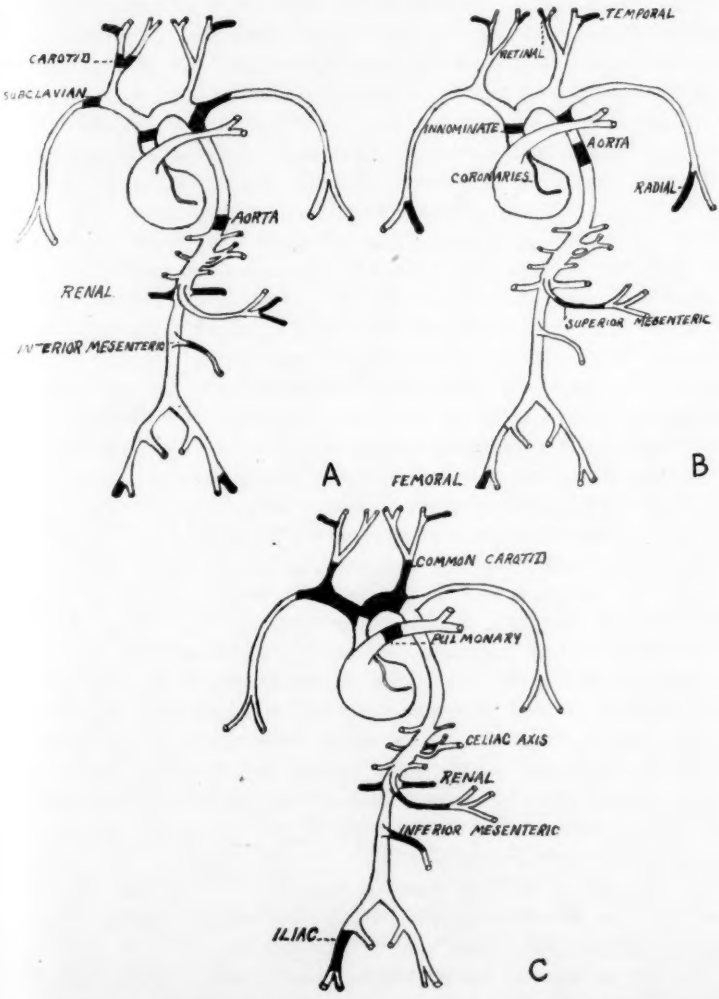

Fig. 16.—The distribution of the arteritis in autopsied cases: *A*, Cooke and others, case 3; *B*, Cooke and others, case 6; *C*, Sproul's case.

response to a single etiologic agent in the acute, subacute, chronic and healed phases of a disease process. The histologic appearance at any

specific time is dependent not only on the character, virulence, concentration, duration of action and site of action of the noxious agent but also on the resistance of the host and the reaction capacity of the particular organ affected. Any attempt, therefore, to correlate histologic pathology with the disease process necessitates the integration of the local lesion and the distribution of such lesions with the general effect on the host and should include the general clinical picture.

In 28 of the 48 reported cases of temporal arteritis the only demonstrable vascular lesions were in one or both of the superficial temporal arteries. Second in frequency of involvement is the central artery of the retina which has always been accompanied by temporal arterial disease on the same side. In relatively few cases have other vessels been studied histologically. There are, however, certain observations which show that this vascular disease is not limited to the temporal arteries and their branches. In the 4 patients who have been examined at the autopsy table vascular lesions similar to those examined in biopsy specimens of the temporal arteries have been found in other vessels of the body (fig. 16). The group of cases reported by Cooke and associates [2] form an important link in the development of our appreciation of this process as a potential widespread vascular disease. Their 7 patients ranging in age from 66 to 73 years all showed inflammatory lesions of the temporal artery. Confirmatory biopsies were performed in 6 of the 7 cases. In 6 cases there were symptoms suggesting a generalized arterial disease. In 2 of these patients this was confirmed by postmortem examination. A characteristic histologic picture was noted in the aorta, temporal, radial, subclavian, femoral, coronary, renal, retinal and mesenteric arteries (fig. 16 *A, B*). In the case reported by Sproul [29] there was involvement of the temporal, carotid, innominate, subclavian, pulmonary, celiac, mesenteric, renal and iliac arteries as well as involvement of the aorta (fig. 16 *C*). In the case reported by Chasnoff and Vorzimer [3] autopsy was said to have revealed changes in other vessels similar to those which had been previously seen in the temporal arteries. The distribution of these lesions has not yet been published.

Although the etiologic agent responsible for temporal arteritis has not yet been demonstrated, the vascular lesions are sufficiently uniform to substantiate the clinical concept that this disease stands apart from other known vascular diseases. In temporal arteritis there in a granulomatous type of reaction involving all coats of the artery, usually greatest in the media. Areas of necrosis are accompanied by a diffuse infiltration of lymphocytes, plasma cells, occasional eosinophils and occasional polymorphonuclear leukocytes. The mononuclear cells seem to predominate

29. Sproul, E. E.: New York State J. Med. 42:345-346 (Feb. 15) 1942.

in the cellular infiltrate. Multinuclear giant cells are conspicuous components of the lesion (fig. 2) although they are vastly outnumbered by the mononuclear cells. The necrosis of the media appears to develop in small foci. Massive necrosis of the media has not been observed. The lesion apparently extends rather slowly and the host is usually able to repair the damaged tissue as the process extends along the vessel. Granulation tissue is formed and is eventually replaced by scar tisue. The cellular reaction apparently depends on the stage of the process. Although many types of inflammatory cells are found it appears significant that mononuclear cells predominate in the picture. Multinucleated giant cells appear to be formed from the proliferating endothelial cells lining the newly formed capillaries. The internal elastic lamina seems to act as a buffer but as an incompletely effective barrier to involvement of the intima. As the process extends through the internal elastic lamina the intima becomes vascularized and fibroblastic proliferation appears stimulated.

With further extension of the inflammatory process into the intima there may be destruction of the endothelial lining and the development of thrombi with obliteration of the lumen. The inflammatory process extending through the periadventitial tissues surrounds but does not appear to penetrate the periarterial nerves. Compression of these nerves by inflammatory tissue may contribute to the excruciating pain of which these patients complain.

It is difficult to evaluate the role of the vasa vasorum in this process. The granulomatous nodules are, for the most part, found in the distribution of the vasa vasorum, i. e. in the media and adventitia. Many of these nutrient vessels reveal striking changes. Some of them show an inflammatory infiltration of their walls, but no fibrinoid necrosis is seen. Some of them have thickened hyalinized walls suggesting a lesion that is of longer duration than that of the surrounding inflammatory reaction. It is possible that the disease process arises in and spreads by way of these nutrient vessels. It is to be noted, however, that the vasa vasorum in close proximity to one another are not uniformly affected but show considerbale variation in histologic appearance.

Phlebitis has rarely been mentioned as a complication of temporal arteritis. In 2 of the cases reported by Horton and Magath [4] there was evidence of phlebitis in one of the retinal veins with the development of hemorrhage and exudates. In case 3 of Cooke and associates [2] there was involvement of the femoral vein with fibrosis and recanalization. No other reports of venous involvement in temporal arteritis have been found. In fact, the absence of phlebitis has been mentioned [19] as one of the points of differentiation between this process and that found in thromboangiitis obliterans. The phlebitis which has been observed in the venae

comites of the temporal artery appears to be a secondary lesion spread by direct extension of the periarterial granulomatous process. The portion of the vein adjacent to the artery may be severely involved while its opposite wall remains intact (figs. 1 and 9). The severe and extensive involvement of the periadventitial tissues leads us to believe that phlebitis will be demonstrated more frequently if the accompanying veins are carefully examined.

It is surprising that no previous reports of temporal arteritis have shown the production of aneurysms. A process which destroys the media with multiple areas of necrosis might be expected to facilitate the development of such a process. The rarity of its occurrence may be due to the marked desmoplastic reaction in the granulomatous tissue, to the tendency for the destructive process to be limited by the internal elastic lamina or to the strengthening of the arterial wall by the collagenous intimal thickening.

Although temporal arteritis appears in an age group in which we expect to find arteriosclerosis, there is nothing in the lesions in most cases of temporal arteritis to suggest that the degenerative lesions of atherosclerosis play a part. In cases 3 and 6 of Cooke and associates [2] arteritis seemed more intense in the region of the atheromatous plaques. They state that in some areas "there seemed to be a combination of atheroma and arteritis." That atherosclerotic lesions have been demonstrated in other vessels in those patients is only to be expected.

There is little to suggest any relationship to tuberculous, syphilitic or rheumatic arteritis. No tubercles, gummas or Aschoff bodies have been associated with the lesions of temporal arteritis. None of the patients have shown positive serologic reactions for syphilis. In none of the cases has there been any evidence of active tuberculosis. The age group, the size of the involved vessels and the paucity of inflammatory lesions in the intima serve to separate the lesions of temporal arteritis from those of rheumatic arteritis.

In thromboangiitis obliterans the large vessels of the lower extremities of young or middle-aged adults are involved by a diffuse panarteritis and phlebitis. In some respects the process is similar to that seen in temporal arteritis. It appears to start in the adventitia and progress through the media to the intima. The steadily progressive process results in thrombosis and obliteration of the arteries and veins with eventual obliteration of the blood supply to the affected part. Giant cells are frequently seen in the granulomatous reaction in the media.

In the acute nonsuppurative arteritis occasionally seen in typhoid fever, scarlet fever, diphtheria and pneumonia the process appears to arise in the intima and is frequently followed by thrombosis. There is usually a subintimal connective tissue proliferation accompanied by an

exudate of mononuclear cells which may extend throughout the vessel wall. Similar lesions may be found in typhus fever, Rocky Mountain spotted fever, disseminated lupus erythematosus, dermatomyositis and in reactions to the sulfonamide compounds. These lesions, however, are usually widespread and are commonly found in the arterioles, smaller arteries and venules. They are characterized by a fibrinoid type of necrosis in which fibrin-like material is deposited in the wall of the vessel. There is usually a perivascular lymphocytic infiltration about the arterioles and venules.

In periarteritis nodosa there is predilection for the muscular type of medium and small size arteries which supply the viscera. This process appears to originate in the adventitia and spreads throughout the wall, producing areas of necrosis in the media. Aneurysms are commonly produced. Thrombosis, rupture and hemorrhage are frequently seen. The cellular exudate depends on the duration of the process. Although polymorphonuclear leukocytes and eosinophils frequently predominate, these cells may be replaced later by plasma cells and lymphocytes. Giant cells are sometimes reported but usually do not form a conspicuous part of the picture. The process tends to be rapidly progressive, and most cases end fatally within a year or two.

The panarteritis seen in extremities subjected to rapid vibration by such instruments as the pneumatic drill is different from that seen in temporal arteritis. In the former there is an extensive infiltration of all coats of the vessel with thrombosis and sometimes recanalization. Recent studies showing the production of arterial lesions by the injection of foreign proteins [30] suggests that a nonspecific arteritis with many of the histologic characteristics of temporal arteritis may be produced experimentally.

Although certain similarities are noted in the histologic structure of the pathologic process of temporal arteritis and in that of other nonsuppurative inflammatory diseases of the arteries, the total picture is sufficiently different to warrant separate classification of this disease process. In some patients many vessels may be involved, but the symtomatology is largely an expression of the involvement of the temporal arteries and sometimes of the retinal arteries. The pathologic process, although not pathognomonic of this disease, is usually distinctive.

Although temporal arteritis is not entirely benign, as Horton, Magath, and Brown [1] originally believed, its relative benignity is borne out by review of the cases thus far reported. In the 43 reported cases plus our 5 cases only seven deaths occurred, one of which we exclude from the disease mortality. This case was first described by MacDonald and

30. Hawn, C.: Personal communication to the authors.

Moser [14] and later by Post and Sanders.[26c]. The patient lived six years after the disease had apparently subsided and died of a cerebral vascular accident. In 1 of Horton and Magath's cases [4] and in Jenning's case 2 [23] the patient died of unrelated causes some time after the temporal arteritis had subsided.

Sproul's [29] patient died of congestive heart failure and pneumonia eight weeks after the onset of his disease. He also had diabetes mellitus and coronary heart disease but, since there was evidence of generalized arteritis, this case has been included as a fatality. Chasnoff and Vorzimer's [3] patient died fourteen months after the onset and three months after the apparent subsidence of temporal arteritis. Postmortem examination showed generalized arteritis, and this case has been included in computing the disease mortality. Among the cases of Cooke and his co-workers [2], cases 3 and 6 showed definite generalized arteritis. In case 2 the patient died shortly after the onset of the disease, and permission for necropsy was not obtained. It was assumed that he died of the disease. These 3 cases are included in computing the disease mortality. Similarly Curtis' [18] patient died three and one half months after the onset of the disease with generalized arteritis and is included as a fatality. This makes a total of six deaths attributed to the disease in 48 cases, or a disease mortality of 12.5 per cent. In comparison with other forms of generalized arteritis this is a very low mortality. Compared with systemic diseases in general in this age group, the process is relatively benign. The fact that it is not entirely benign should, however, be recognized.

All methods of treatment to date have been ineffective with the exception of section of the temporal arteries. The therapeutic measures which have been tried are: administration of salicylates, and of liver by mouth and injection, potassium and sodium iodide, arsenic, mercury, "prontosil" (azosulfamide), sulfanilamide, sulfathiazole, vitamins A, B complex, and D, acetophenetidin, cobra venom, amyl nitrite and nicotinic acid, and finally section of the temporal vessels. In 1 case [31] the Sanders oscillating bed was used with apparent improvement in that case. Biopsy was first utilized for diagnostic purposes but was found useful for therapy. Section of the temporal arteries may be done easily under local anesthesia. Two or 3 cm. of the artery should be resected between ligatures together with the vein and the perivascular sympathetic nerve fibers close to the origin of the artery but above the branches to the masseter muscle and the temporomandibular joint (fig. 15). This is also above the site of origin of the transverse facial artery and the middle temporal artery. It

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31. Schaefer, C. L., and Sanders, C. E.: Am. Heart J. 24:410-411 (Sept.) 1942.

corresponds to the area of skin just anterior to the superior margin of the pinna of the ear. Interruption of the perivascular sympathetic nerve fibers has been given as the reason for relief of local symptoms. In most cases relief of headache, local pain and tenderness has been obtained after section of the affected vessels. At times it is dramatic, as it was in our case 2. The systemic symptoms are not relieved by this procedure, however, and they usually persist for what would presumably correspond to the natural course of the disease.

The homogeneity of the cases thus far reported warrants classification of temporal arteritis as a distinct disease entity. Horton, Magath, and Brown [1] chose to await observation of more cases before the "condition is dignified by nomenclature." The question has been raised, notably by Dantes [22], Cooke and associates [2] and Kilbourne and Wolff,[19] whether or not "temporal arteritis" is too restrictive a term for a disease characterized by such obvious and definite systemic manifestations. Kilbourne and Wolff [19] suggested the term "cranial arteritis," which would, however, be open to the same criticisms as "temporal arteritis." Whether a name indicative of the systemic nature of the disease should be adopted at this time is also open to question. The nomenclature of diffuse vascular inflammatory diseases, especially of the lupus erythematosus disseminata, dermatomyositis, periarteritis nodosa group or generalized "vascularitis" is already inadequate. While it is true that temporal arteritis probably represents a much more widespread vascular disease than the name indicates, the inflammation of the temporal arteries has thus far remained the constant and dominant feature of the disease. Until etiologic classification is possible retention of the simple descriptive term "temporal arteritis" is suggested.

SUMMARY AND CONCLUSIONS

Two cases of temporal arteritis are presented in detail. Three additional cases are briefly reported. The essential data of all the previously reported cases are presented and analyzed.

The pathologic changes in biopsy specimens of artery segments of 1 of our cases are described in detail. A dissecting aneurysm of one temporal artery and phlebitis of the accompanying veins were found. The pathology of the disease in general is discussed.

From the analysis and study of the clinical and pathologic data of all the reported cases certain facts are apparent.

(*a*) Temporal arteritis is a distinct clinical entity affecting people of the older age group and characterized by local symptoms consisting of painful, tender, red, swollen, nodular and thrombosed temporal arteries with edema and pain in the adjacent structures and systemic symptoms consisting of fever, malaise, anor-

exia, loss of weight and weakness. The edema of the overlying skin is probably contributed to by phlebitis of the accompanying vein.

(*b*) Blindness is relatively common in this disease and was found in one or both eyes in 33.3 per cent of the cases. The possible prophylactic value of section of the middle temporal artery early in the disease is suggested.

(*c*) The local symptoms can be reasonably explained on the basis of inflammation of the temporal vessels and their branches.

(*d*) The systemic symptoms probably indicate a more generalized arteritis.

(*e*) The mortality of this disease, 12.5 per cent, is considerably less than that of most other forms of arteritis.

(*f*) The cause of the disease is unknown.

(*g*) Since the involvement of the temporal vessels and the symptomatology arising from it are constant and dominant features of the disease, it is suggested that the term "temporal arteritis" be retained until etiologic classification is possible.

THROMBOSIS OF THE INFERIOR VENA CAVA DUE TO HYPERNEPHROMA

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AND
NORTON D. RITZ, M.D.
BROOKLYN

THE CASE herein described is reported because of three cardinal points: first, the relative frequency with which dilated abdominal veins due to cirrhosis of the liver were mistaken for those due to obstruction of the inferior vena cava; secondly, the unusual venous thrombosis that extended from the femoral veins through the inferior vena cava to the right auricle of the heart, and lastly, because increased awareness of this condition may lead to its more frequent diagnosis.

REPORT OF A CASE

The patient was a 70 year old white man, first admitted to a hospital on Aug. 27, 1946, with edema of the legs for three weeks. He also had noted occasional pain in the left upper abdominal quadrant for several months. He had had gonorrhea about forty-five years previously and admitted having been a heavy beer drinker until twenty years ago. There were no other pertinent facts disclosed at this time.

Physical examination revealed the following symptoms: There were a few crepitant rales at the base of the left lung. The heart was somewhat enlarged to the left, and the blood pressure was 152 mm. of mercury systolic and 78 mm. of mercury diastolic. Occasional extrasystoles were noted. The liver was palpated 5 fingerbreadths below the right costal margin and was somewhat tender. The tip of a mass thought to be spleen was palpated below the left costal margin. There was a well developed collateral circulation over the abdomen, more pronounced along the flanks than around the umbilicus. Edema of the ankles (2+) was present.

The diagnosis at that time was arteriosclerotic heart disease and possible cirrhosis of the liver.

The patient was placed on a cardiac regimen of digitalis and diuretics, after which the rales in the lungs rapidly disappeared. Edema of the ankles persisted. The cephalin flocculation, alkaline and acid phosphatase contents, phosphorus level and blood were normal at this time. Total plasma protein was 6.4 Gm. per hundred cubic centimeters. The veins of the abdominal wall were noted to fill from below. Despite therapy, the liver did not decrease in size. An electrocardiogram was interpreted as indicative of "myocardial damage." A punch biopsy of material from the liver was reported to reveal "congestion of the liver." The urine was normal.

Two weeks later the patient signed his release from the hospital. The diagnosis on discharge was "cirrhosis of the liver." Four days later, on Oct. 8, 1946, he was admitted to Kings County Hospital. His complaints were considerable dyspnea and weakness. At this time he gave a history of having had dyspnea and pedal edema

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for three months. He also had noted a dull, inconstant pain in the left upper and left lower abdominal quadrants. The pain was not related to meals or to defecation. He again gave a history of fairly heavy alcoholism.

Physical examination revealed an emaciated, dyspneic, rather anemic man 70 years of age who had evident weakness. There was slight distention of the veins of the neck. Moist rales were present at the base of the right lung. The heart tones were regular but of poor quality. No murmurs were present. The blood pressure was 150 mm. of mercury systolic and 84 mm. of mercury diastolic. A firm edge of liver was felt 4 fingerbreadths below the right costal margin. A mass thought to be spleen was palpated in the upper abdominal quadrant 4 to 5 fingerbreadths below the left costal margin. The abdominal veins were distended and were most prominent along the lateral region of the abdominal wall and the flanks. These veins filled rapidly from below. No caput medusae was present. There was edema (2+) of the legs and feet. Rectal examination did not reveal any hemorrhoids or masses.

The diagnosis was hepatosplenomegaly, probably due to hepatic cirrhosis, and arteriosclerotic heart disease.

Laboratory Studies.—The urinalysis disclosed a specific gravity of 1.018, a trace of albumin and a few casts and white blood cells per high power field. The hemoglobin content was 8 Gm. per hundred cubic centimeters as determined by the Sahli method. The peripheral blood count revealed 4,300,000 red blood cells per cubic millimeter; the white blood cells numbered 14,200, with 70 per cent neutrophilic polymorphonuclear cells, 25 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophilic polymorphonuclear cells. The circulation time (arm to tongue with triketocholanic acid) was fourteen seconds (normal range, eight to sixteen seconds). The reaction to a Wassermann test of the blood was negative. At this time the blood urea was 42 mg. and the fasting blood sugar 88 mg. per hundred cubic centimeters and the alkaline phosphatase 5.6 units (normal range, 2 to 8 units). The reaction to the cephalin flocculation test was negative on two occasions. The total blood cholesterol level was 200 mg. per hundred cubic centimeters, with 125 mg. as cholesterol esters and 75 mg. as free cholesterol.

During the following month the value for the total cholesterol esters was 126 mg. per hundred cubic centimeters, with 67 mg. of cholesterol esters and 59 mg. of free cholesterol. The total plasma protein was 5.8 Gm. per hundred cubic centimeters, with 3.4 Gm. of albumin and 2.4 Gm. of globulin. One week later the total plasma protein was 6.2 Gm. per hundred cubic centimeters, with 3.8 Gm. of albumin and 2.4 Gm. of globulin. The icteric index was 4. The blood phosphorus level was 4 mg. per hundred cubic centimeters.

An electrocardiogram showed depression of the S-T segments in leads II and III, consistent with digitalis effect and myocardial damage.

A roentgenogram of the chest revealed an irregular nodule in the left midpulmonary field, which was interpreted as a possible metastatic lesion. The osseous system, including the extremities, spine, skull and pelvis, was free from metastasis. A roentgenogram made after barium enema showed no obstruction or intrinsic lesion in the colon. A roentgenogram of the esophagus did not reveal esophageal varices.

Course in the Hospital.—On October 15 the patient first noted dark-colored urine. He complained of frequency and dysuria. Careful questioning disclosed that he had had a similar attack of hematuria for a short period about one year ago. The urine gave a positive reaction to the benzidine test and contained albumin (1 plus) and numerous casts, red blood cells and white blood cells.

Three days later a cystoscopy was performed. The prostatic urethra was elongated. There was protrusion of the lateral lobes (1 plus) and a median bar (2 plus). The mucosa of the bladder showed trabeculation (1 plus).

In view of the gross hematuria and of the cystoscopic findings, the mass in the left upper quadrant noted on the previous examination was reevaluated at this time. It was now thought to be the left kidney rather than the spleen. Perirenal air studies confirmed this impression (fig. 1).

On October 24 an intravenous pyelogram was made and two days later a retrograde pyelogram.

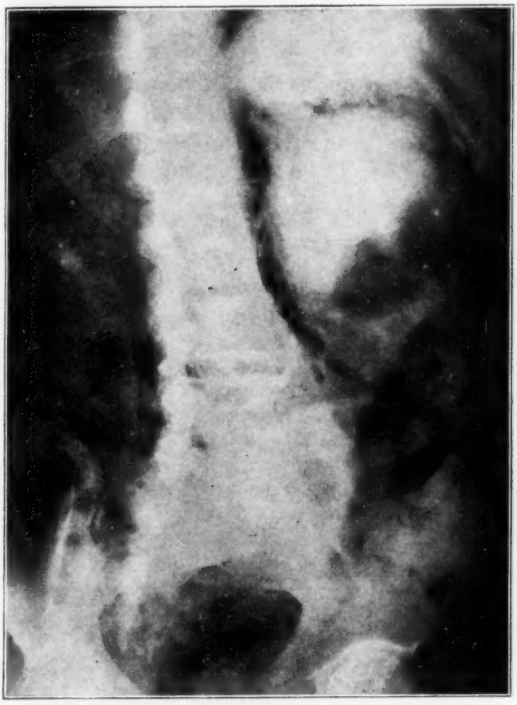

Fig. 1.—Perirenal air study showing large tumor of the left kidney.

On cystoscopy, the left ureteral orifice was somewhat inflamed. A no. 4 catheter passed easily up the right ureter for a distance of 25 cm. On the left side an obstruction was encountered 2 cm. from the ureteral orifice. Phenolsulphonphthalein dye appeared on the right side after five minutes, while on the left there was none apparent after ten minutes.

Retrograde pyelography revealed that there was enlargement of the left kidney and tortuosity of both ureters, particularly the left. There was no irregularity or dilatation of the calices or pelvis of the right kidney. However, the left kidney showed poor filling, with a persistent filling defect in the pelvis and in the upper 3

cm. of the ureter. The conclusion was that the patient had (1) bilateral ptosis of the kidneys and (2 a space-occupying lesion of the left kidney, the pelvis and the upper part of the left ureter, possibly on the basis of a papillary intrapelvic growth (fig. 2).

The hematuria gradually subsided. However, frequency and some dysuria persisted. The urine repeatedly contained a trace of albumin (1 plus) and variable numbers of red and white blood cells. The enlargement of the collateral veins became more prominent on the back as well as on the lateral part of the abdomen and chest.

Studies of the blood were undertaken to discover if there was any systemic bleeding tendency. The blood coagulation time by test tube method was five

Fig. 2.—Intravenous urogram. The left kidney shows enlargement and poor filling, with persistent filling defect within the pelvis and the upper 3 cm. of the ureter.

minutes, the bleeding time thirty seconds and the clot retraction time normal. The platelets numbered 140,000 per cubic millimeter. The prothrombin time was fifteen seconds, with a control of fourteen seconds. A Rumpel-Leed cuff test elicited a strongly positive reaction. The white blood cells numbered 11,200 per cubic millimeter, with a normal differential count. The hemoglobin content was 6 Gm. per hundred cubic centimeters as determined by the Sahli method. Two blood cultures were sterile. The findings pointed to an increased capillary fragility. A transfusion of 500 cc. of blood was given.

On November 1 a femoral venipuncture for pressure readings was attempted bilaterally but was unsuccessful. The venous pressure in one of the dilated abdominal

veins, namely, the right inferior superficial epigastric vein, was taken. At a point 1 inch (2.5 cm.) above the inguinal ligament the venous pressure was 13 cm. of water. The circulation time from this vein to the tongue, determined with the use of triketocholanic acid, was 14.5 seconds, demonstrating a fairly efficient collateral circulation.

It was thought at this time, in view of the persistent edema of the lower extremities, the pronounced collateral circulation over the abdomen, flanks, back and chest and the presence of a large renal mass with hematuria, that the entire picture

Fig. 3.—Venogram showing block of the femoral vein and the dilated collateral abdominal veins. A wooden ruler was compressed over the abdomen to prevent the "diodrast" from flowing into the collateral abdominal veins and to encourage the flow through the deep veins. Despite this compression, the dye did not enter the femoral vein.

could be explained by the presence of a hypernephroma of the left kidney growing into the left renal vein and the inferior vena cava, with obstruction down to the femoral veins.

Because of the age, the general poor condition of the patient and the probable involvement of the right renal vein, operative intervention was decided against.

During the next week, the edema over the lower extremities continued to increase. The abdomen appeared slightly distended, and the patient complained of vague abdominal pains. Repetition of the studies of the blood revealed the following: The bleeding time was one minute and the coagulation time determined by capillary

tube method was four minutes. The hemoglobin content was 9.5 Gm. per hundred cubic centimeters by the Sahli method, the red blood cell count was 4,100,000 per cubic millimeter and the white blood cells number 8,500 per cubic millimeter, with a normal differential cell count. The prothrombin time was thirteen seconds, with a control of thirteen seconds. The reaction to the Rumpel-Leed cuff test was now normal.

During the next two weeks, the edema of the legs decreased somewhat but persisted enough to obscure most of the veins.

Venipuncture of the femoral veins was again unsuccessful on November 26. The impression that both veins were thrombosed was strengthened.

A week later it was noted that the edema of the lower extremities had decreased still more but that the abdominal collateral circulation was now more prominent. No caput medusae was present.

On December 5, 20 cc. of 70 per cent "diodrast" was successfully injected into the left saphenous vein while roentgenograms were taken simultaneously. The phlebogram thus obtained revealed that the contrast medium did not enter the femoral vein but coursed directly into the superficial circumflex iliac, superficial epigastric, and lateral femoral cutaneous veins to anastomose with the dilated abdominal veins despite pressure applied over the latter. This finally confirmed the clinical impression of thrombosis of the femoral vein (fig. 3).

The patient continued to go gradually downhill. Gross hematuria periodically manifested itself. On Dec. 12, 1946, he died.

Abstract of Autopsy Protocol.—The body was that of a poorly developed, extremely emaciated 70 year old white man measuring 64 inches (162 cm.) in length and weighing approximately 80 pounds (36 Kg.). Along the lateral walls of the chest and over the flanks there were distended veins of a mean diameter of about 4 mm. The veins of the neck were not distended. The abdomen was flat; in the left upper quadrant a firm irregular mass was palpable.

The right lung weighed 400 Gm. and the left lung 350 Gm. A firm yellowish white nodule 1.5 cm. in diameter was present in the anterior portion of the upper lobe of the left lung. No other metastasis was noted in either lung.

About 1 cm. below the origin of the right pulmonary artery the lumen of the vessel branch to the right lower lobe was dilated and occluded by an adherent yellow-gray firm thrombus. Hilar and tracheobronchial lymph nodes were small and anthracotic.

The heart was opened while still attached to the arterial and venous trunks (fig. 4). The right auricle contained the terminal portion of a tumor thrombus which extended into it from the inferior vena cava. The left ventricle was somewhat dilated and its wall thickened. The coronary vessels were moderately sclerotic but patent throughout their course.

The right kidney was normal in shape and consistency. It appeared somewhat larger than usual, measuring 11 by 7 by 7 cm. The left kidney was the site of a firm and, for the most part, discrete large tumor mass which measured 19 by 19 by 10 cm. It was embedded in a rather large amount of adrenal fat, which was readily separated from the surrounding tissue. The renal veins were markedly distended and filled by yellowish gray soft tumor tissue. The caliber of the veins reached 2 cm. Section through the mass revealed that almost the entire upper pole of the kidney was replaced by a yellow hemorrhagic soft tumor. The pelvis of the kidney was dilated, displaced downward and partially occupied by the mass. The mucosa was deep red and spongy; protruding into the ureter was a polypoid, rubbery, yellow-gray tumor cast of the pelvis. The ureter was slightly dilated throughout

its course and of a maximum diameter of 0.5 cm. In addition to the renal vein, the suprarenal and inferior phrenic veins were packed with tumor tissue. The inferior vena cava was solidly filled with a tumor resembling a long sausage beginning at the level of the renal vein and extending into the right auricle. However, the tumor did not invade the hepatic veins, which emptied into a channel between the thrombus and the wall of the inferior vena cava. The portion of the vena cava

Fig. 4.—Autopsy specimen shows both kidneys sectioned. The tumor of the left kidney is on the right side. The inferior vena cava and the heart are above. The iliac veins are thrombosed below. This shows the tumor thrombus distending the lumen of the inferior vena cava and extending upward into the right auricle of the heart.

and its tributaries below the renal vein, including the left spermatic vein, was totally occluded by a reddish gray organized thrombus.

The fatty tissue surrounding both kidneys contained numerous dilated thin-walled blood vessels, indicative of collateral circulation emptying into the retroperitoneal venous plexus.

The urinary bladder was thick walled and contracted. The surface of the mucosa was hyperemic and partly hemorrhagic, and it contained yellowish gray purulent material. The openings of the ureters were small. The right ureter was normal in caliber throughout. The left ureter was dilated. The prostate was moderately

enlarged; numerous small concretions were present. There were some thromboses in the prostatic plexus.

The spleen was normally firm. There appeared to be an increase in the fibrous tissue. One calcific nodule 2 mm. in diameter was present at the upper pole. The splenic vein was slightly dilated.

The liver weighed 1,400 Gm. It was firm and deep brownish. Cut surfaces showed a nutmeg appearance. Scattered throughout the liver were nine discrete ovoid whitish yellow metastatic nodules of a maximum diameter of 1 cm. The hepatic veins were wide and free of tumor or thrombi.

The right adrenal was small. The medulla was thick and well preserved, with mottled light grayish areas in the central portion. The left adrenal was situated on top of the main tumor mass. Its surface presented the same appearance as that of the right.

The remaining gross findings were compatible with the age of the patient.

Microscopic Examination.—There was slight fibrosis of the myocardium and minimal fibrous thickening of the endocardium. The metastasis seen in the lungs in the gross examination was confirmed. The spleen had fibrous thickening of the capsule, which was diffusely infiltrated with small round cells. The pulp was congested. The calcific nodule noted grossly contained amorphous pink-blue material surrounded by a fibrous wall. The liver showed chronic passive congestion; the central veins and sinusoids were congested, with atrophy of hepatic cells.

The nodules seen grossly consisted of metastatic cells. In the adrenals numerous small discrete cortical adenomas and cortical hyperplasia were present. Within the medullary portion were tumor cells. Section of the right kidney revealed moderate congestion, with several small wedge-shaped subcapsular areas of fibrous and round cell infiltration. An occasional glomerulus was hyalinized. There was slight hyaline thickening of the intima of the blood vessels.

Section through the left kidney in the region of the tumor revealed considerable compression and congestion of the parenchyma, with some round cell infiltration. The tumor tissue was arranged in large lobules separated by a fairly thick irregular layer of fibrous tissue. The tumor tissue was seen distending the large blood vessels. The tumor cells were large and for the most part clear, but many had eosinophilic cytoplasm and were arranged in irregular cords, with a suggestion of papillation. The nuclei were large, pleomorphic and hyperchromatic, with occasional atypical mitotic figures and bizarre forms.

The mucosa of the bladder was congested and in part desquamated. There was diffuse round cell infiltration. The prostate contained numerous laminated eosinophilic and basophilic cells. Round or oval masses were present in the acini. There was some glandular and stromal hyperplasia. Many acini were distended with exudate consisting of polymorphonuclear leukocytes, with some infiltration of adjacent tissues. There was moderate squamous metaplasia. The seminal vesicles were normal. Organized canalized thrombi were seen in some of the blood vessels.

Anatomic Diagnosis.—The anatomic diagnosis was adenocarcinoma of the left kidney (hypernephroma), with metastasis to the liver, lungs and adrenal gland, invasion by the tumor to the left renal vein, the inferior vena cava, the inferior phrenic vein, the left suprarenal vein, the right atrium, the left renal pelvis and the left ureter, thrombotic occlusion of the inferior vena cava and its tributaries into both femoral veins, chronic passive congestion of the liver, calcific nodule in the spleen, pyelitis of the left kidney, cystitis and arteriosclerosis, adenomatous hypertrophy of the prostate, bilateral hydrocele, cerebral edema and cardiac hypertrophy.

The cause of death was considered to be adenocarcinoma (hypernephroma) of the left kidney.

COMMENT

Recent observations in World War II and in civilian practice have made physicians more aware of occlusions of the inferior vena cava. In the last ten years at Kings County Hospital 151 cases of hypernephroma have been noted; 104 of the patients were males, and 47 were females. It was surprising to note the relative paucity of case reports in the literature in the last ten years as compared with those in previous years. Attention should again be directed to reemphasize the relative frequency of this clinical picture. Pleasants [1] reported in 1911, after an exhaustive study of the material to that date, that there were 322 cases of obstruction of the inferior vena cava described in the medical literature. In 21 of these the condition was due to carcinoma or hypernephroma of the kidney. Taddei,[2] Squire [3] and others [4] reported cases of obstruction of the inferior vena cava due to hypernephroma extending into the right auricle. However, among all these cases only 1 demonstrated obstruction down to the femoral veins such as occurred in the case described here.[5]

In 1924 Judd and Scholl,[6] of the Mayo Clinic, reported 15 cases of hypernephroma with obstruction of the inferior vena cava. They showed that of 200 cases of renal tumors the renal vein was involved in 45, or 22.5 per cent. Nephrectomy and removal of the plug of tissue from the renal vein and beyond proved the only hopeful approach to treatment at the Mayo Clinic. Donovan [7] resected a short length of the inferior vena cava in removing a hypernephroma of the right kidney.

The cause of obstruction of the inferior vena cava has been thoroughly discussed by Pleasants.[1] He grouped all known cases under the following etiologic factors: (1) thrombosis, (2) new growths arising from the wall of the vessel, (3) invasion of the lumen by growths from without, (4) pres-

1. Pleasants, J. H.: Obstruction of the Inferior Vena Cava, with a Report of Eighteen Cases, John Hopkins Hosp. Rep. **16**:363-548, 1911.

2. Taddei, D.: Patologia e clinica dei tumori del rene, Folia urol. **2**:638-700, 1908.

3. Squire, J. B.: Neoplasm of Kidney and Ureter, Boston M. & S. J. **161**:547-551, 1909.

4. Johnson, S. E., and Stabile, V.: Hypernephroma with Metastases, Kentucky M. J. **41**:351-352 (Oct.) 1943. Abeshouse, B. S., and Goldstein, A. E.: Metastatic Malignant Tumors of the Kidney: Review of Literature and Report of Twenty-Three Cases, Urol. & Cutan. Rev. **45**:163-186 (March) 1941. Stevens, W. E.: Diagnosis and Surgical Treatment of Malignant Tumors of the Kidney, J. Urol. **10**:121-134 (Aug.) 1923.

5. Schrag, A. R., and Jordan, F. B.: Unusual Metastasis for Primary Hypernephroma, Canad. M. A. J. **53**:168-169 (Aug.) 1945.

6. Judd, E. S., and Scholl, A. J.: Thrombosis and Embolism Resulting from Renal Tumors, J.A.M.A. **82**:75-78 (Jan. 12) 1924.

7. Donovan, H. A.: A Malignant Right Kidney Removed at Operation, Together with Short Length of Vena Cava, Brit. J. Urol. **17**:107 (Sept.) 1945.

sure from without by neoplastic or inflammatory disease and (5) so-called congenital obliteration of the inferior vena cava.

In general, there are four primary routes of collateral circulation: inferior vena cava to superior vena cava, inferior vena cava to portal veins, portal veins to superior vena cava and inferior vena cava to inferior vena cava around the obstruction. Northway and Greenway [8] have demonstrated the extensive retroperitoneal and paravertebral collateral veins of the inferior vena cava by injection methods.

The cardinal signs of obstruction, edema and collateral circulation also vary in degree. Edema may not develop if death occurs rapidly. Occlusion of the lower third of the inferior vena cava is less likely to be associated with edema than occlusion a block higher up. In typical cases edema lessens with the development of an adequate collateral circulation. It is striking how little functional impairment or discomfort may occur when collateral circulation is well developed. In the patient described here, with an obstruction extending at autopsy from the femoral veins through the iliac vessels and the inferior vena cava to the right auricle, edema persisted for almost four months. It disappeared only in the last week before death. As the edema decreased, the abdominal collateral veins became much more prominent.

When the obstruction extends high enough to obstruct the hepatic veins, ascites or, more rarely, jaundice may develop. In the present instance, although the tumor thrombus extended into the right auricle there was a channel alongside the thrombus enabling the hepatic veins to empty.

In differentiating obstruction of the inferior vena cava from obstruction of the portal vein there are a number of helpful points. Unless the hepatic veins are obstructed, the collateral circulation about the umbilicus is seldom as well defined in the former as in the latter. A caput medusae is a rarity. The collateral veins in obstruction of the inferior vena cava predominate along the lateral region of the abdomen, the lateral area of the chest, the back and the iliac and inguinal regions. In obstruction of the portal vein the collateral veins tend to group near the midline, particularly between the umbilicus and the xiphoid process. Hemorrhoids or esophageal varices are not ordinarily present in obstruction of the inferior vena cava. However, when the obstruction involves the left renal vein, a varicocele on the left side which persists when the patient is in a supine position is positive evidence in its favor.

A last supplementary differential aid, as demonstrated in this case, is the performance of venography, which may demonstrate the lowermost point of obstruction and the collateral circulation.

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8. Northway, R. O., and Greenway, C. D.: Vena Cava and Its Collateral Circulation, Univ. Hosp. Bull., Ann Arbor **10**:67-69 (Sept.) 1944.

When distended collateral veins are noted on the abdomen, the possibility of an obstruction existing in the inferior vena cava must be entertained. A consideration of the location of the main collateral veins often enables the differential diagnosis from obstruction of the portal vein to be made. In this connection, the frequency with which hypernephroma involves the inferior vena cava is of great importance.

SUMMARY

1. A review of the literature reveals over 400 cases of obstruction of the inferior vena cava.

2. The case reported demonstrates the possibility of confusing cirrhosis of the liver with obstruction of the inferior vena cava because of dilated abdominal veins.

3. The unusual extension of thrombosis involving the femoral veins up through the inferior vena cava to the right auricle due to hypernephroma is reported.

4. It is important in all cases of dilatation of the abdominal veins to rule out the diagnosis of obstruction of the inferior vena cava. More extensive use of venography, with abdominal compression as a diagnostic adjunct, is to be encouraged.

135 Fenimore Street (Dr. Fisher).

PNEUMONIA ASSOCIATED WITH ACUTE SALMONELLOSIS

Report of a Case of Salmonella Bronchopneumonia and Fourteen Cases of Interstitial Pneumonia

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IN A RECENT report [1] of an outbreak of food poisoning due to Salmonella montevideo in an army general hospital in North Ireland note was made of bronchopulmonary involvement in 19 (6 per cent) of the 350 persons affected. One of the patients had frank bronchopneumonia, with sputum which contained the Salmonella organism. Others had interstitial pneumonia, and their sputum did not contain the organism. The cases in which there were respiratory manifestations are given more detailed consideration in the present communication.

The outbreak affected 350 persons in a three day period from April 11 to 14, 1944. The immediate source of infection was rice pudding allowed to stand at kitchen temperature for twelve hours or more, and the evidence indicated that the cook who prepared the pudding was a carrier of the organism. Besides the aforementioned bronchopulmonary changes, the clinical manifestations included pronounced gastrointestinal upset, severe prostration and toxicity, high fever, herpes febrilis (15 per cent), bacteremia (2 cases), neuritis, cutaneous lesions (urticaria and subcutaneous nodules) and an asthenic phase. There were no deaths. Agglutinins against the Salmonella organism (in titers up to 1:800) and against sheep's red blood cells (in titers up to 1:512) were found in the serums of some of the patients tested.

Of the 19 patients with bronchopulmonary manifestations, 4 had mild cough during or shortly after the gastroenteritic phase of the

1. D'Albora, J. B.; Ingegno, A. P., and Edson, J. N.: Outbreak of Food Poisoning Due to Salmonella Montevideo in an Army General Hospital, J.A.M.A. **129**:10 (Sept. 1) 1945.

illness. There were no clinical or roentgenographic evidences of pneumonia, and the condition was interpreted as bronchitic.

One patient had definite bilateral bronchopneumonia, with sputum which contained S. montevideo. His history follows.

REPORT OF A CASE OF SALMONELLA BRONCHOPNEUMONIA

Private F. T. R., a white man 21 years old and belonging to the Field Artillery, was admitted to the surgical service of the 79th General Hospital on March 2, 1944, because of internal derangement of the left knee. An arthrotomy was performed on April 4, 1944. Except for an occasional rise of the temperature to 99 F. there was no fever or gastrointestinal disturbance from March 21 to April 12, 1944. On

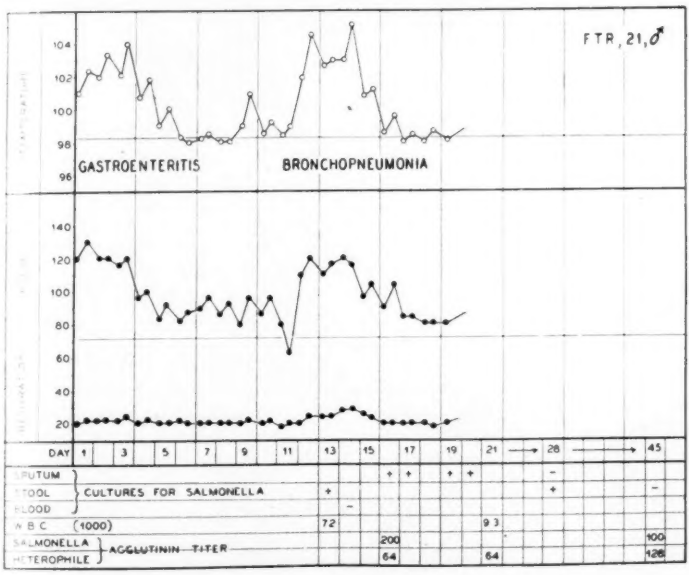

Fig. 1.—Temperature chart and salient laboratory findings in a case of salmonella bronchopneumonia.

April 12 at 2 a.m., nine hours after a supper which included infected rice pudding, diarrhea, abdominal cramps, headache, general malaise, nausea and vomiting suddenly developed. The patient became extremely toxic, with the temperature going as high as 104 F. on the third day. Herpes labialis appeared. There were five watery stools the first day, and the diarrhea lasted five days in all.

After an initial febrile period of five days, fever and toxicity abated for three days although moderate tachycardia continued. There was then mild fever for two days. On April 22, ten days after onset of the gastroenteritis, the patient complained of chilliness, severe generalized headache (especially frontal), general aching, cough and sharp pain in the upper left anterior part of the chest exaggerated by deep breathing and cough. The temperature rose sharply, reaching a maximum of 105.2 F. three days later (fig. 1). Examination revealed severe toxicity and prostration, tachycardia and moderate respiratory difficulty. There was an impaired note, with high-pitched bronchovesicular breath sounds and a few crepitant rales,

over the left lung anteriorly. The sputum became frankly bloody. A roentgenogram (fig. 2*A*) on April 24 showed a bilateral bronchopneumonic process, especially in

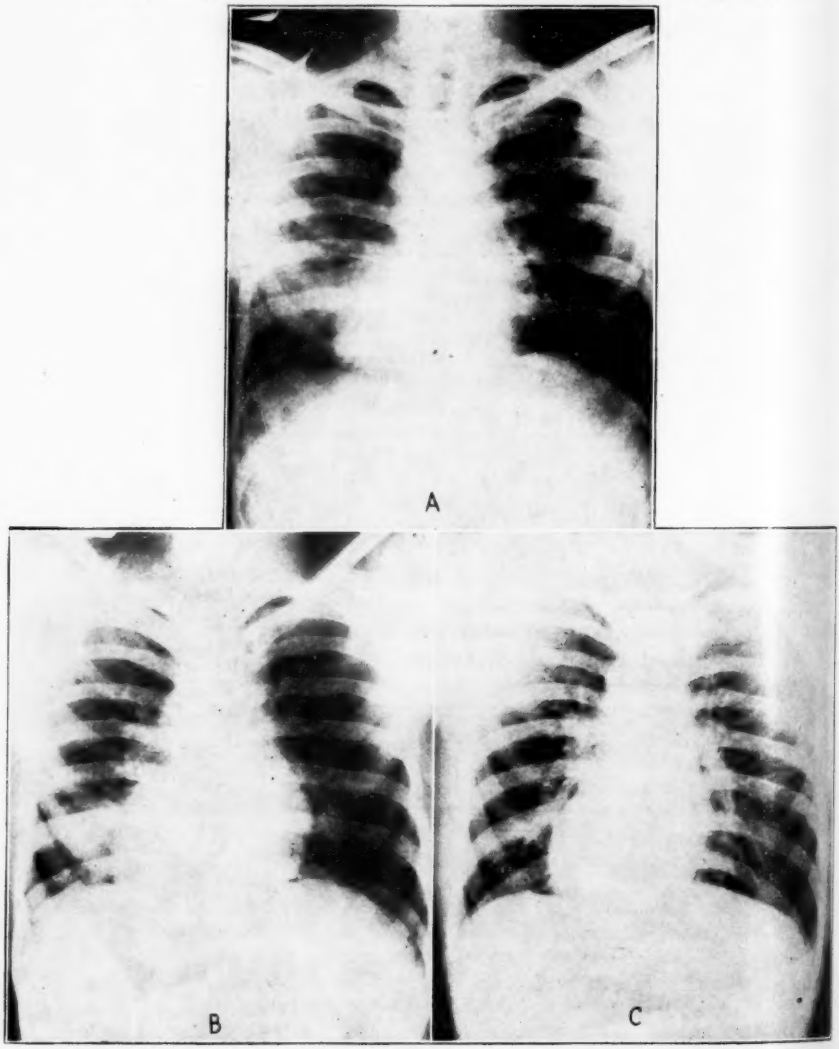

Fig. 2.—*A*, Salmonella bronchopneumonia (third day). The process is bilateral, with a confluent patch in the left lower pulmonary field. The pleura on the left is thickened. *B*, same patient on the seventh day. There is partial resolution of the bronchopneumonic process. Pleuritis is still evident. *C*, same patient on the thirteenth day. There is almost complete resolution.

the lower left pulmonary field, where there was a large confluent patch. The pleura on the left was thickened, and interstitial changes were seen on the right.

The stool contained S. montevideo, and four cultures of the sputum made between April 27 and May 1 also yielded the organism. The white blood cell count and the differential count were within normal limits. On April 27 the serum showed Salmonella agglutinins in a titer of 1:200 and heterophile agglutinins (to sheep's red blood cells) in a titer of 1:64.

The patient was severely ill for five days, with hemorrhagic sputum and with severe pain in the left side of the chest. For three of these days the temperature ranged between 103 and 105.2 F. The temperature then fell rapidly to normal on the seventh day. The respiratory symptoms subsided considerably although the pain in the chest was troublesome for a week. Three subsequent roentgenograms taken up to a month later (figs. 2*B* and *C*) showed progressive resolution. The last of these, taken on May 23 (not illustrated), showed complete resolution. The sputum remained frankly bloody for about a week and then became mucopurulent and scant. On May 9 culture of the sputum showed it to be sterile although the stool still contained the Salmonella organism. A month after the onset of the respiratory complication there were still slight cough and slight pain in the left upper part of the chest. At this time Salmonella agglutinins in a titer of 1:100 and heterophile agglutinins in a titer of 1:128 were found in the serum. At no time was the spleen palpable and there were no cutaneous lesions analogous to rose spots. However, an interesting symptom in this patient was the appearance on April 23, at the height of the bronchopneumonic episode, of three small subcutaneous nodules on the anterior aspect of the left thigh and one on the volar aspect of the right forearm. The former disappeared in a day, but a month later the one on the forearm was still present. It was 2 to 3 mm. in diameter, slightly tender but not discolored, and it was attached to fascia but not to the overlying skin.

During the gastrointestinal phase of his illness the patient received 57 Gm. of sulfaguanidine over a three day period, with no obvious effect on the course of his illness. Treatment was otherwise entirely symptomatic. Experience with other patients in the outbreak had not demonstrated any appreciable effect on the infecting organism by either sulfaguanidine or sulfadiazine. Hence neither sulfonamide was given during the period of bronchopneumonia.

The remaining 14 patients reported on in this paper had clinical and roentgenographic evidence of interstitial pneumonia. The main features are summarized in the appended tabulation.

Salient Findings in 14 Patients with Interstitial Pneumonia Accompanying Acute Salmonellosis Due to Salmonella Montevideo

Acute gastroenteritis . . . Initial phase in all. Lasted 2 to 8 days. Stool cultures positive for S. montevideo
Quiescent interval between gastroenteritic and bronchopulmonary phase . . . Present in 8 cases, lasting 1 to 4 days. In 6 the two phases overlapped
Symptoms . . . Recurrence or exacerbation of fever and toxicity in all. Cough in 13 cases. Expectoration in 8 cases (in 4 mucoid, in 4 bloody or blood streaked). Chest pain in 3 cases
Pulmonary signs . . . Found in 11 cases, generally mild. Rales and changes in breath sounds and resonance
Duration of bronchopulmonary phase . . . 4 to 14 days, average 10 days. Fever lasted 3 to 10 days
Sputum cultures . . . Done 1 to 3 times in 8 cases. All negative for Salmonella. Usual mouth organisms
Blood cultures . . . Positive for Salmonella in 2 of 8 patients tested
Blood counts . . . Not characteristic
Serum Salmonella agglutinins . . . In titers ranging from 1:50 to 1:800
Heterophile agglutinins (8 cases) . . . In titers ranging from 1:32 to 1:256
Roentgenologic findings . . . Patchy or diffuse interstitial pneumonitis in all. Bilateral in 8, on right side only in 6. Partial consolidation in 2. Pleuritis in 1. Resolution complete within 2 weeks in almost all

All the patients were young white men who had been hospitalized for a variety of reasons. They were all afebrile prior to the outbreak of Salmonella infection. In all the initial acute gastroenteritic phase of

the illness was typical of what occurred in the general outbreak. There was an explosive onset eight to fifty hours after ingestion of the infected rice pudding, with fever, toxicity, prostration, abdominal cramps and watery diarrhea. This phase lasted two to eight days.

In 8 of the 14 cases there was then a quiescent interval of one to four days, characterized by absence or considerable diminution of fever, toxicity and gastrointestinal complaints. There then followed a secondary rise in the temperature, increased toxicity and bronchopulmonary complaints, which came on five to nine days after the onset of the illness. In the remaining 6 cases the quiescent interval was not as clearly defined. There was on overlapping of the course of fever and the gastrointestinal and bronchopulmonary symptoms, although in some the appearance of pulmonary symptoms was accompanied with an exacerbation of the fever and toxicity. In 2 of these the blood cultures yielded the Salmonella organism. One patient, after being afebrile for a day, had a recurrence of fever, and although he had no symptoms or physical signs of pulmonary involvement, there was definite roentgenologic evidence of interstitial pneumonia. One patient with frank evidence of pneumonia beginning on the second day and lasting for about two weeks had fever for only three days from the onset.

Of the 14 patients, 13 had symptoms and/or signs of pulmonary infection which began two to nine days (in 10 cases five to nine days) after onset of the gastroenteritis. All 13 had cough varying from mild to severe, and in 8 the cough was productive. The sputum was blood streaked or frankly bloody in 4 and mucoid in 4. Three patients had pain in the chest; it was substernal in 2 and over the left side of the chest in the other. There were physical signs in the lungs in 11 patients. Unilateral or bilateral coarse rales were heard in 6 cases. The percussion note was impaired in 4 patients; there were diminished breath sounds in 2 and harsh breath sounds in 1. Crepitant rales were noted in 3 cases. In 7 the physical signs were confined to the right side while in 3 there were no local physical signs of pulmonary involvement. It is thus evident that the regional signs were relatively mild and probably arose mainly from bronchial inflammation. They were in no case suggestive of consolidation. This is in keeping with the nature of the roentgenographic pattern.

The duration of bronchopulmonary manifestations varied from four days to two weeks, with an average of ten days. In the 7 cases in which the high temperature attributable to the pneumonitis could be defined with reasonable clarity it lasted from three to ten days and reached maximums of 100.4 to 105 F. The pulse rate was proportionately elevated except in 1 case, in which it was relatively slow and dicrotic. The patient in this case had a respiratory rate of 36, although in most of the others there was only a mild tachypnea.

The sputum was cultured one to three times in 8 cases. In none could Salmonella be found. There were only the usual mixtures of organisms of the mouth, with no one type predominant. In 7 cases the white blood cell count during the bronchopulmonary phase varied from 6,500 to 24,000, with polymorphonuclear cells ranging from 33 to 80 per cent and lymphocytes from 19 to 67 per cent. The changes in the white blood cell count could not be clearly correlated with the clinical course. Nor, in fact, did any distinctive change in the count occur with the onset of the pneumonia when compared with the findings during the period of gastroenteritis. The total white blood cell count and the percentage of polymorphonuclear cells would rise or fall indiscriminately. Generally speaking, however, the more prolonged the illness as a whole,

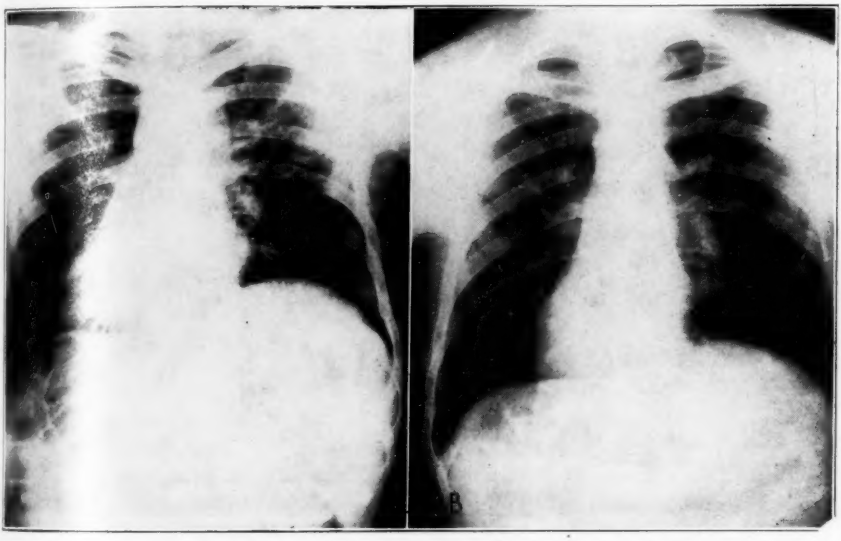

Fig. 3.—*A*, patient with acute salmonellosis. Moderately severe interstitial pneumonia with partial consolidation in the upper lobe of the right lung. *B*, same patient four days later. Resolution is almost complete.

whether or not it was accompanied with pulmonary inflammation, the greater was the tendency to leukopenia and to relative lymphocytosis.

In all the cases cultures of the stool yielded S. montevideo at some time during the course of the illness. The onset of bronchopulmonary complaints did not characteristically affect the length of time for which the cultures of the stool were positive. In 2 cases, as already noted, the blood cultures revealed S. montevideo. In 6 other cases blood cultures were sterile. In 4 cases urine cultures were also sterile.

Salmonella agglutinin titers in the serum ranged from 1:50 to 1:800, and in 8 patients tested heterophile agglutinin titers ranging from 1:32 to 1:256 were found. The time of appearance, the intensity and the duration of these reactions were not characteristically affected by the presence of bronchopulmonary involvement.

Roentgenologic examination of the chest showed changes interpreted as indicative of interstitial pneumonia in all 14 patients. In 8 the changes were bilateral while in 6 the right side only was affected; in 3 the upper lobe of the right lung was affected, in 1 the lower lobe of the right lung and in 4 the entire right side. These interstitial changes were patchy or

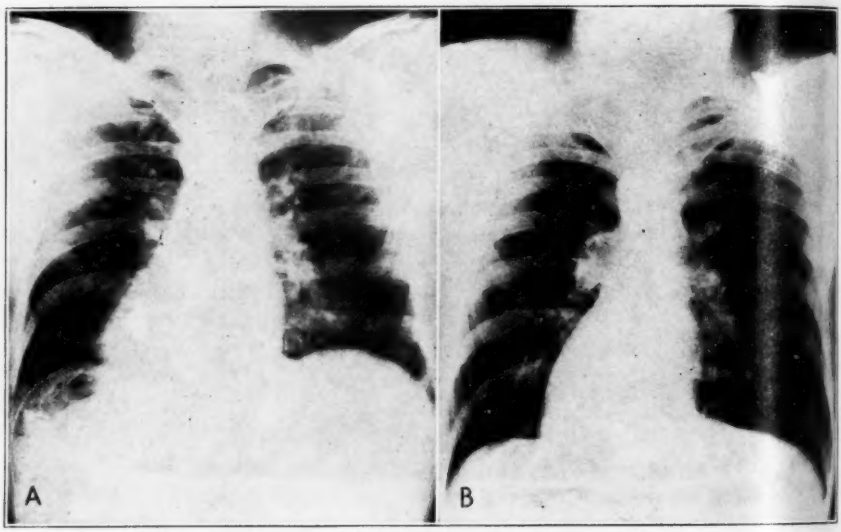

Fig. 4.—*A*, patient with acute salmonellosis. Interstitial pneumonia of the right lung with basal pleuritis, *B*, same patient seven days later. Interstitial and pleuritic changes are resolved.

diffuse and in 2 instances were accompanied with partial consolidation. In 1 patient there was evidence of pleuritis at the base of the right lung. Resolution began within four to seven days of onset and in almost all was complete in about two weeks. There were neither clinical nor roentgenologic evidences of any suppurative complication. The roentgenologic changes found in 2 of the patients are illustrated in figures 3 and 4.

A scattering of other symptoms and signs included asthenia, general malaise, anorexia, herpes labialis, chills, aches and pains, neuritic pains and dysesthesias, sweats and transient urticaria. Sulfaguanidine (39 to 96 Gm.) given during the gastrointestinal phase in 8 patients had no

apparent effect. Sulfadiazine (32 to 42 Gm.) was tried during the pneumonitic phase in 3 patients and was also without result.

COMMENT

The variability of the manifestations of salmonellosis has been amply documented in the various reports of outbreaks as well as in reports of isolated cases. Sachs and Antine[2] have recently reviewed the different types and reported five illustrative cases. The three broad groupings of Salmonella infection include the gastroenteric type, Salmonella fever (clinically simulating typhoid fever) and the septicopyemic type. The last type has come to be recognized as offering a particularly important diagnostic problem, for the cases frequently occur as isolated examples entirely unrelated to any outbreak of gastroenteritis, and almost any viscus or body structure may be affected. The symptoms and signs may thus be extremely variable, depending on the area of localization of the Salmonella organisms. Suppurative phenomena are common.

Pulmonary involvement in salmonellosis, however, has received scant consideration. Bullowa[3] in 1928 reported a case of infection of the lung with Bacillus suipestifer (hog cholera). His patient had consolidation of the middle lobe of the right lung. There was a severe febrile course for five days, with moderate leukocytosis. Sputum and blood cultures and postmortem puncture of the lung yielded a growth of the organism. Cohen, Fink and Gray[4] in 1936 reported an instance of pericarditis, pneumonitis and pleural effusion in a patient whose blood culture twice yielded S. suipestifer. There was no note of the organism being obtained from cultures of material from other areas of the body. In 1 of the cases reported by Sachs and Antine the blood culture contained S. suipestifer, and the findings at autopsy included septic bronchopneumonia with pulmonary abscesses and empyema. It is not clear from the report whether cultures of material from the local lesions were made.

It may be assumed that true Salmonella bronchopenumonia with pulmonary consolidation, such as is reported here, is probably a relatively rare manifestation of salmonellosis. The diagnosis is established by demonstration of the offending organism in the sputum or by puncture of the lung. It is most likely that the organism reaches the lung through

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2. Sachs, J., and Antine, W.: Salmonella Infection in Man, Am. J. M. Sc. **208**:633 (Nov.) 1944.

3. Bullowa, J.: Bacillus Suipestifer (Hog Cholera) Infection of the Lung, M. Clin. North America **12**:691 (Nov.) 1928.

4. Cohen, L.; Fink, H., and Gray, I.: Salmonella Suipestifer Bacteremia with Pericarditis, Pneumonitis and Pleural Effusion: Report of Case, J.A.M.A. **107**:331 (Aug. 1) 1936.

the blood stream, although the possibility of aspiration is not entirely excluded. The development of pulmonary suppuration, as in Sachs and Antine's case, represents a more serious complication of the septicopyemic variety of salmonellosis in which there may be widespread abscess formation as in other types of pyemia. Whether or not suppuration complicates the picture the role of the Salmonella germ in causing the local pulmonary lesion in Salmonella bronchopneumonia is fairly obvious.

The exact relation of the Salmonella infection to the more numerous instances of interstitial pneumonia discussed here is not so apparent. Repeated cultures of the sputum failed to demonstrate the organism. The clinical and roentgenologic similarity to so-called atypical pneumonia is evident. Since at the time the outbreak occurred there was also a fairly high incidence of the latter ailment among the troops stationed in the area, it may well be that these cases merely represent the result of an entirely unrelated etiologic agent (virus?), ubiquitously distributed, gaining a foothold in patients rendered susceptible by the debilitating effect of the Salmonella infection. Nevertheless, it is also possible that the interstitial pneumonia of salmonellosis in man represents a condition analogous to that occurring in the hog, in which a specific virus is associated with the Salmonella infection. Naturally one cannot exclude entirely the possibility, however unlikely, of a remote toxic or allergic effect of the presence in the body of the Salmonella organism. The entire question deserves careful consideration in any future outbreak of salmonellosis should the opportunity present itself for exhaustive roentgenologic, bacteriologic and viral investigation.

SUMMARY

In an outbreak of acute salmonellosis due to Salmonella montevideo 19 patients (6 per cent) had evidence of bronchopulmonary involvement. Four had acute bronchitis. One patient (reported on in detail) had definite bronchopneumonia, with sputum which contained the Salmonella organism. The other 14 patients had interstitial pneumonia. The pathogenesis of the interstitial type is unknown, but the clinical and roentgenologic features suggest a viral origin. How frequently interstitial pneumonia occurs in Salmonella outbreaks generally and whether or not, if a virus is concerned, it is of a specific type are points worthy of consideration by future investigators.

CYTOCHROME C THERAPY OF TISSUE ANOXIA IN A CASE OF HEPATOLENTICULAR DEGENERATION

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IN SEPTEMBER 1946 there was admitted to our service a patient with a bizarre clinical syndrome. He presented the symptoms of well advanced parkinsonism, with masklike facies, open mouth with drooling saliva, cogwheel rigidity of musculature, festination of gait, anarthria and a tremor which was present at rest and which was accentuated on intention. The Babinski response was present bilaterally. Clubbing of the fingers and toes was prominent, the skin showed decided pigmentation of generalized distribution and there was edema of the lower part of the legs. The liver and spleen were palpable. Petechiae were present, and there was constant oozing of blood from the gums as well as intermittent microscopic hematuria. Increased bleeding time, total failure of clot retraction and increased capillary fragility, with a relatively normal platelet count were observed. A striking finding was the intermittently bright red color of the venous blood, which resembled arterial blood.

Five months later the patient was found to have developed the Kayser-Fleischer ring of pigmentation at the corneoscleral junctions, said to be pathognomonic of Wilson's disease.[1] Clubbing has not previously been described in this disease, nor have the hematologic findings here presented, though bleeding has occurred in late stages of the disease in association with severe hepatic damage.

The bright venous blood and the presence of clubbing seemed to us to point toward the existence of a relative anoxia. The heart and the lungs were essentially normal, and the vital capacity was unimpaired. In the arterial blood there was normal oxygen saturation of the hemoglobin.

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From the Medical Service and the Biochemical Laboratory, Winter Veterans Administration Hospital.

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1. Denny-Brown, D.: Hepatolenticular Degeneration, in Diseases of the Basal Ganglia and Subthalamic Nuclei, New York, Oxford University Press, 1946, p 302 (1)-(21).

Spectroscopic study of the blood pigment did not reveal the presence of abnormal forms of hemoglobin. Urinary studies for various metallic poisons and for porphyrins were consistently noncontributory.

We were left, therefore, with the theory of a disturbance of tissue oxidation to account for the patient's anoxia (the "histotoxic type" of anoxia, although we were by no means certain that a toxin was involved rather than an intrinsic metabolic fault). That the patient was anoxic was confirmed by repeated determinations of the arteriovenous oxygen difference, which was found to vary within a narrow range of hypoxia, of which the most extreme was manifested clinically by the bright red color of venous blood. Consistent with the concept of a reduced total of tissue oxidation was the low basal metabolic rate (—24 per cent) in the presence of a presumed normal level of thyroxin as suggested by normal rates of circulation and normal cholesterol levels. We supposed originally that the low level of oxygen utilization by the tissues might account for the widespread manifestations of otherwise unaccountable dysfunctions present.

At this point it may be pertinent to present a simple scheme of tissue oxidations as these are currently understood.[2] In the following formula (adapted from Peters, J. P., and Van Slyke, D.D.: Quantitative Clinical Chemistry, ed. 2, Baltimore, Williams & Wilkins Company, 1946, vol. 1, p. 124) we have outlined what is probably the most important pathway, in a quantitative sense, of enzymatic cellular respiration. Each

$$\text{Substrate } H_2 \rightarrow 2H^+ + 2e + \text{oxidized substrate (Catalyzed by specific dehydrogenase)}$$

$$2H^+ + 2e + \text{Coenzyme I} \rightarrow \text{Coenzyme I } H_2$$

$$\text{Coenzyme I } H_2 + \text{Flavoprotein} \rightarrow \text{Coenzyme I} + \text{Flavoprotein } H_2$$

$$\text{Flavoprotein } H_2 + 2 \text{ Cytochrome } Fe^{+++} \rightarrow \text{Flavoprotein} + 2 \text{ Cytochrome } Fe^{++} + 2H^+$$

$$\text{Cytochrome } Fe^{++} + \text{Cytochrome Oxidase } Fe^{+++} \rightarrow \text{Cytochrome } Fe^{+++} + \text{Cytochrome Oxidase } Fe^{++}$$

$$1/2\ O_2 \rightarrow O^{--} + 2(+)$$

$$2 \text{ Cytochrome Oxidase } Fe^{++} + 2(+) \rightarrow 2 \text{ Cytochrome Oxidase } Fe^{+++}$$

$$O^{--} + 2H^+ \rightarrow H_2O$$

metabolite is oxidized with the catalytic aid of its specific dehydrogenase, with one of the two co-enzymes (diphosphopyridine nucleotide and triphosphopyridine nucleotide) serving to accept the liberated hydrogen ion. The co-enzymes are in turn reoxidized by a reaction involving catalytic reduction of another respiratory enzyme, one of the flavoproteins, which then takes up the hydrogen ions. The flavoprotein (yellow enzyme or cytochrome reductase) is in turn reoxidized by one of the cytochromes.

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2. Wynne, A. M.: Intracellular Oxidation and the Biological Transformation of Energy, in Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945, pp. 323-336.

The cytochromes, of which there are at least three, designated *a*, *b* and *c* by Keilin, function in series, each reoxidizing the one before it, until finally the last is reoxidized by cytochrome oxidase, the respiratory enzyme of Warburg. These enzymes differ from those which have gone before in that they do not take up the hydrogen ions. Instead, they shuttle between the ferric and ferrous states, while the hydrogen ions, remaining relatively free within the surrounding aqueous medium, transfer their electric allegiance. The cytochrome oxidase, having been itself reduced by reoxidizing the last of the cytochromes, has the unique power of reoxidizing itself by ionizing molecular oxygen in the surrounding medium. The ionic oxygen then combines with the hydrogen to form water.

In the course of these reactions, there becomes available to the cell the energy predictable from the chemical structure of the original substrate. This energy is liberated in stepwise fashion as each reaction climbs higher in the oxidative scale. The steps involving the cytochromes account for more than two thirds of the total energy released by this chain of reactions, as indicated by the oxidation-reduction potentials of the enzyme systems. Of the energy thus made available, approximately two thirds are lost in the form of heat (which serves also to maintain body temperature) and one third is utilized in the metabolic activities of the tissue cells. Energy not immediately utilized is stored in the form of energy-rich phosphate bonds, chiefly adenosine triphosphate and creatine phosphate, compounds which function to store and transfer such energy in the form of phosphates to be utilized in the metabolic flux of the earlier catabolism and the anabolism of the foodstuffs and of such vital functions as muscular contraction and glandular secretion.

We had no means of determining where in this scheme our patient's metabolic fault might lie, though such determination would be at least theoretically possible with proper enzymatic studies of tissue in a Warburg apparatus. It did seem, however, that we might influence the kinetics of the entire series of enzymatic oxidative reactions by introducing one or more of these enzymes. Such studies had, in fact, been carried out by Proger and Dekaneas,[3] who demonstrated both in men and in animals that the anoxic effects of breathing 10 per cent oxygen could be eliminated by injections of cytochrome *c*. (In a later study on animals, Scheinberg and Michel,[4] using 3.9 and 2.8 per cent oxygen, were unable to confirm this effect of cytochrome *c*. However, we are of the opinion that the anoxia which they produced was too extreme; cytochrome may improve the utilization of marginal quantities of available oxygen, but it can hardly substitute for that essential gas).

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3. Proger, S., and Dekaneas, D.: The Use of Cytochrome C in Combating Tissue Anoxia, Science **104**:389 (Oct. 25) 1946.

4. Scheinberg, H., and Michel, H. O.: The Effects of Cytochrome C in Anoxia, Science **105**:365 (April 4) 1947.

We therefore prepared cytochrome *c* (using the method of Keilin and Hartree[5]) from equine hearts, purified it by passage through a Seitz filter and administered it to our patient after preliminary testing. Cytochrome *c* is the only one of the cytochromes which is easily extracted and stable. Minced cardiac tissue is its richest source, from which it is extracted with dilute trichloracetic acid; it is then fractionated with ammonium sulfate and precipitated with trichloracetic acid, to be obtained finally as a dark red solution containing approximately 1 per cent protein. The cytochromes are similar structurally to hemoglobin, consisting of an iron-porphyrin complex conjugated with a protein.

In Proger and Dekaneas's experiments 50 mg. of the drug had sufficed for reversing the anoxic effects of breathing 10 per cent oxygen. They claimed that there was absorption of the injected drug by the tissues, with release into the blood stream of any unneeded excess. Such excess was easily determined by the pink color produced in the plasma, which is not unlike the appearance of slightly hemolyzed blood. It was this effect which we aimed at as an indication that a state of sufficiency had been reached. Our patient seemed to require unusually large amounts, since we observed this effect only intermittently while using 80 mg. or more daily intramuscularly.

Since submission of this paper, a report has appeared which serves to explain our difficulty in obtaining a pink color in the patient's serum (Rabinovitch, R.; Elliott, K. A. C., and McEachern, D.: Cytochrome C: Intravenous Administration in Man, J. Lab. and Clin. Med. **33**:294 (March) 1948). These authors suggest that the pink color of serum observed by Proger and Dekaneas after injection of cytochrome *c* may have been due to the presence of hemoglobin as a result of slight hemolysis. Cytochrome *c* in serum could be detected by hand spectroscope only within thirty minutes of injection of 500 mg. In vitro, concentrations of at least 6.5 mg. per hundred cubic centimeters were required for spectroscopic detection. Pinkish discoloration of serum required a concentration of about 20 mg. per hundred cubic centimeters. Discoloration of urine required doses of 200 mg. injected intravenously.

In addition to cytochrome *c*, our patient was given 3 Gm. of sodium succinate daily since succinic acid has been shown by Szent-Györgi to participate in another pathway of oxidative metabolism leading up to the cytochrome series. In this pathway, certain dicarboxylic acids function as oxidation-reduction systems to carry hydrogen atoms from the dehydrogenase system to the cytochrome system. Succinic acid $CH_2COOH.CH_2COOH$ is oxidized to fumaric acid CHCOOH: CHCOOH, with concomitant reduction of the cytochrome, and the fu-

5. Keilin, D., and Hartree, E. F.: Purification and Properties of Cytochrome C, Biochem. J. **39**:289, 1945.

maric acid is reduced to succinic acid by taking up the hydrogen liberated from the substrate by its dehydrogenase. Proger was able to demonstrate an antianoxic effect of succinate when it was used alone and a potentiating effect when used with cytochrome *c*; these effects were minor in comparison with that of the cytochrome.

We also used large amounts of vitamin B complex, with the intention of increasing the vitamin precursors of the co-enzymes (nicotinic acid) and of the flavoproteins (riboflavin).

REPORT OF A CASE

Case History Prior to Cytochrome Therapy.—The patient was apparently well until May 1943, when he was hospitalized for five weeks while in the army, with a diagnosis of influenza. This occurred in California; he had not been overseas. From May until his next hospitalization in September, 1943, he lost 30 pounds (13.6 Kg.) in weight, felt weak, tired and nervous, had pains in his legs, joints and muscles and tremor of the hands, slept poorly, had frequent headaches and giddiness and pains in the chest and was restless, anxious and tense. Examination on his admission revealed nothing abnormal except small varicose veins. During his course in the hospital, he complained mainly of numbness of the body and showed no improvement. Studies of the blood and urine were noncontributory, and no fever occurred. The diagnosis in October was severe neurasthenia following influenza, and the patient was granted a medical discharge from the service. Edema of the ankles was noted at this time as well as a prolonged P-R interval, tachycardia and a systolic murmur. In view of these findings, the diagnosis was changed from post-influenzal neurasthenia to rheumatic myocarditis.

After his discharge from the army the patient was able to hold a job as assistant manager of an automobile supply store until Jan. 1, 1946, when he stopped work because of increasing frontal headache, weakness and intermittent fever. Since then he had become rapidly worse, with difficulty in speech, tremor of the left hand, general stiffness and slowing of all muscular movements and drooling from the mouth. Slight swelling of the ankles had been present continuously for the past three years. He was admitted to Winter Veterans Administration Hospital, Topeka, Kans., on Sept. 26, 1946. His weight was 158 pounds (71 Kg.); the maximum weight prior to the initial illness had been 218 pounds (99 Kg.). The family history and the past history were noncontributory; no familial instances of diseases of the liver or brain or of bleeding diseases were uncovered.

On examination, the patient was found to be a well developed and well nourished white man who was 30 years old and over 6 feet (183 cm.) tall and who appeared chronically ill. His face presented a fixed expression, with the mouth open. There were few spontaneous movements of the extremities. Slowness of gait and tremor of the left hand were present. The breath was fetid. The head, neck and chest were otherwise normal. The pulse rate was 70 and regular and the blood pressure 140 mm. systolic and 90 mm. diastolic. (The blood pressure never varied during the patient's subsequent course.) The heart was normal in size, the tones were normal and there was a soft systolic murmur at the apex. The edge of the liver was palpable and smooth, and it was not tender. A small scar was seen on the dorsum of the penis. Clubbing of all fingers and toes was present, manifested by parrot beaking of the nails and by bulbous enlargement of the terminal phalanges. Slight pitting edema of both ankles and of the lower part of the legs and widespread pigmentation of the entire body surface (most notable on the lower part of the legs) were noted. A slight tremor was present in the right hand and a more pronounced one in the left; the tremor was noted to be sometimes of the intention type and sometimes of

the nonintention type. Pill-rolling movements of the fingers and thumb of the left hand were present. Tendon reflexes were exaggerated throughout, and the skin

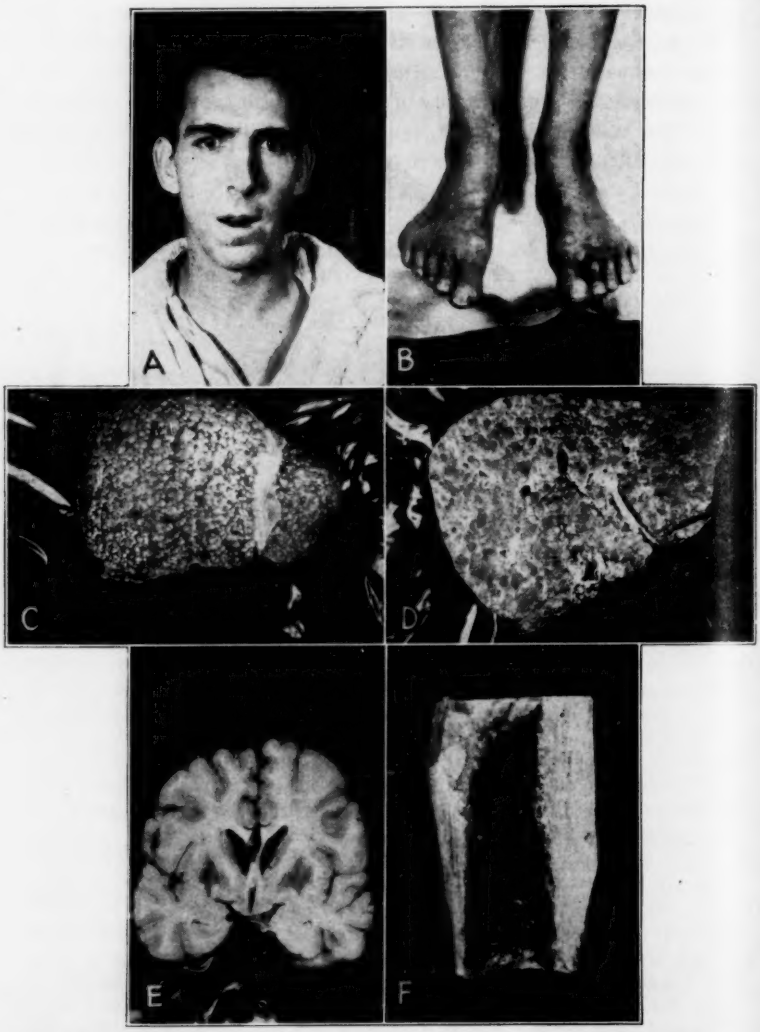

Fig. 1.—*A*, parkinsonian facies. *B*, clubbing of the toes and pigmentation of the skin. Some edema is evident. *C*, ventral aspect of the liver surface, showing extreme degree of nodular cirrhosis. *D*, cut surface of the liver. *E*, brain sectioned through the lenticulostriate nuclei. Note involvement of the internal and external capsules in the widespread degeneration of the lenticulostriate areas. *F*, bone marrow of the femur, with the dark red appearance of hematopoiesis.

reflexes were intact. The Babinski sign was present bilaterally, with dorsiflexion of the great toe and fanning of the others. No changes in the sensory or cranial

nerves were present. There was cogwheel rigidity of the musculature, but weakness of the muscle was not severe. The patient was unable to speak above a whisper. He was passive and uncomplaining and cooperative within his ability. Intelligence appeared unimpaired, but emotional lability was evident.

Bleeding from the gums appeared a few days subsequent to his admission to the hospital and continued intermittently. On October 5 a crop of petechiae was found at the bases and sides of the toes of both feet and a few were found in the palms of the hands; these gradually faded and disappeared in the course of two weeks. Tourniquet compression produced a considerable crop of petechiae at the elbow. The patient stated that he had had previous crops of petechiae during the past year. The prothrombin time was normal. The blood plasma ascorbic acid level was normal (1.1 mg. per hundred cubic centimeters). The circulation time was normal (calcium, 14 seconds). Large doses of vitamins B, C and K had no effect on the bleeding from the gums. Repeated urinalyses revealed intermittent microscopic hematuria, with occasional cellular and granular casts, and traces of albumin. Blood counts showed a moderate anemia, with the red blood cell count averaging 4,000,000 per cubic millimeter and the hemoglobin content 12.5 Gm. per hundred cubic centimeters (color index was approximately 1.0). The hematocrit reading was 38.5 volumes per cent and the corrected sedimentation rate 8 mm. per hour (Wintrobe method). The white blood cell count averaged 6,500 per cubic millimeter; the differential distribution was normal, the eosinophil count varying from 2 to 4 per cent. Platelet counts were 190,000, 180,000 and 150,000 per cubic millimeter. Clotting times were five and a half, eight and six minutes; bleeding times were six and a quarter, five, one and a half and four minutes. The clot retraction in twenty-four hours was repeatedly minimal or absent. A study of red cell fragility showed beginning hemolysis with 0.40 per cent and complete hemolysis with 0.28 per cent sodium chloride. Smears of the sternal bone marrow did not appear unusual. The spleen became palpable, though the palpability may have been missed on initial examination.

The vital capacity was over 100 per cent. The basal metabolic rates were —20 and —24 per cent. Two glucose tolerance tests showed normal fasting blood sugar levels, with a rise to 200 mg. in two hours and a delayed fall, which suggested difficulty in storage or in utilization of glucose. Reactions to Kolmer and Kahn serologic tests were repeatedly negative; a blood culture revealed no pathogenic organisms. The serum protein was 6.2 Gm. per hundred cubic centimeters, with a normal albumin-globulin ratio. The bilirubin content was 0.15 mg. per hundred cubic centimeters. The cholesterol and cholesterol ester values were 167 and 80 mg. respectively and the blood urea nitrogen levels 22.4 and 12 mg. per hundred cubic centimeters. The blood chloride content, as sodium chloride, was 520 mg. per hundred cubic centimeters on two determinations. The serum calcium was 10.8, inorganic phosphorus 3.2 and 2.1 and potassium 16.5 mg. per hundred cubic centimeters. The acid-soluble organic phosphorus content of the serum was 0.6 mg. per hundred cubic centimeters. Studies of the spinal fluid, including culture for tubercle bacilli, revealed no pathogenic organisms, no increase in protein or cell content, a negative reaction to the serologic test for syphilis and a normal colloidal gold curve.

Venous blood oxygen levels at times when the blood was bright red were 15, 15.4 and 14.2 volumes per cent, and when it was blue they were 12 and 12.1 volumes per cent. (Blood oxygen volumes as determined by us represent oxygen combined with hemoglobin exclusive of dissolved plasma oxygen; the figures for total blood oxygen would be approximately 0.3 per cent higher.) On occasions when arterial blood oxygen was not determined simultaneously with the venous oxygen careful determinations with the Fisher electrohemoglobinometer were made and the expected value calculated; these calculated values did not differ appreciably from those ac-

tually determined. Venous circulation times were determined simultaneously to insure a normal rate of circulation at the time of the determinations of oxygen levels. Carbon dioxide—combining power was determined once on red venous blood and found to be 44 volumes per cent and once on blue venous blood and found to be 53 volumes per cent.

Tests for urinary bromides and for various heavy metals[6] did not reveal any. Results of tests for porphyrinuria were repeatedly negative. No creatine was found in two twenty-four hour specimens; creatinine outputs in twenty-four hours were 1.57 and 0.4 Gm. Urea and chloride outputs in twenty-four hours were within normal limits, and the Kepler excretion test for Addison's disease gave a negative result. Phenolsulfonphthalein output was 27 per cent in one hour and 25 per cent in the second hour, a total of 52 per cent.

Concentration tests gave low normal values (1.019). Urine culture yielded Staphylococcus albus, believed to be a contaminant. Inoculation of a guinea pig with urine produced negative reactions. Gastric analysis on two occasions yielded normal volumes of free and total acid.

Laryngoscopy disclosed normal vocal cords, with sluggish action, indicating weakness of the musculature but no paralysis. The ocular fundi were normal. The visual fields showed peripheral contraction, more pronounced for color. Kayser-Fleischer rings at the corneoscleral margins were discovered in February after having been looked for and found absent the previous October. Roentgenograms of the chest, stereoscopic roentgen study of the skull and roentgenograms of the bones of the extremities revealed no abnormalities. Electrocardiograms showed prolonged (0.22 second) and slightly varying P-R intervals and minor changes in the forms of the P and T waves. Biopsy of the skin and muscle revealed an increase in the connective tissue of the dermis, vacuolization and thinning of the epithelium, pigmentation of basal epidermal cells (which gave a negative reaction to the test for iron) and thickening of the media of arterioles due to an increase of connective tissue. There were no perivascular infiltrations, nor was there any indication of cellular exudate elsewhere. The muscle fibers had a glazed appearance. An intravenous injection of 5 cc. of adrenal cortex extract failed to change the bright red color of the venous blood.

The patient had no fever during this period of hospitalization except once during the course of an infection of the upper respiratory tract of short duration and terminally. At one time a series of hemorrhagic blebs appeared on the right thigh; cultures and smears of these revealed no organisms, and they slowly healed.

Subsequent Course.—On November 29 cytochrome *c* therapy was started, 80 mg. being given daily intramuscularly. The patient seemed to improve clinically within a few days. It is perhaps difficult to state with assurance that the parkinsonian manifestations improved because of the cytochrome *c* therapy, since the intensity of symptoms in parkinsonism is commonly observed to vary with the patient's mood. Furthermore, remissions have been described in cases of Wilson's disease. However, in view of the patient's rapid and unaltered downhill course prior to therapy and the absence of effect of the usual medications used in parkinsonism, we deem his course to have been at least considerably slowed. After two months of continuous therapy, he was able to speak aloud, to feed himself and to walk unassisted. Tremor and cogwheel rigidity disappeared, though plastic rigidity remained. The patient no longer noticed flickering of the motion pictures shown at

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6. Metals of groups II and III were looked for in twenty-four hour samples of urine concentrated ten times. These included mercury, lead, bismuth, copper, cadmium, arsenic, antimony, tin, aluminum, chromium, iron, nickel, cobalt, manganese and zinc.

the hospital, a difficulty formerly present. Edema of the lower part of the legs disappeared (for the first time in three years), and pigmentation and clubbing both diminished notably. The patient's facial expression became more mobile, his mouth remained closed, his tongue was less thickened and no longer encrusted with dried blood and drooling of saliva ceased. The liver became smaller (though this may have represented an advance in the cirrhotic process of Wilson's disease), and the spleen was no longer palpable.

Hemorrhagic manifestations diminished notably but not completely at first. The bleeding time was no longer prolonged (three, two and a half and one second), and the clot retraction was now normal (repeatedly complete in two hours). Clotting times were unchanged (three and one-sixth, four and four seconds). Capillary resistance was improved but still subnormal; bleeding was now confined to oozing from the gum margins, and even this was considerably reduced. Administration of 120 mg. of rutin[7] daily was then added to the patient's therapy on January 27; by February 10 the gums were dry and capillary resistance was normal. A single blood platelet count was 100,000; however, at this time the patient no longer bled. Corrected sedimentation rates were 6 to 16 mm. per hour. Hematocrit readings varied from 35 to 41 volumes per cent.

Icteric indexes of 10 and 7 were found. The blood urea nitrogen was 16 mg. and the nonprotein nitrogen 35 mg. per hundred cubic centimeters. The blood cholesterol level was 153 mg. and the ester level 94 mg. per hundred cubic centimeters. Prothrombin time remained normal. The serum protein was 5.7 Gm., with 3.2 Gm. of albumin and 2.5 Gm. of globulin, per hundred cubic centimeters. The glucose tolerance test now gave a fasting level of 127 mg., with a rise to 250 mg. in one hour and a return to 121 mg. in four hours and to 67 mg. in five hours. The cephalin flocculation test gave a reading of 4 plus in twenty-four hours. The sulfobromophthalein test showed 5 per cent retention in twenty-five minutes. The hippuric acid test resulted in excretion of 1.7 Gm. The patient's metabolic rate reverted to

E. T. LOWE— VOLUMES PER CENT OF BLOOD OXYGEN

	Normal	Hemoglobin 12.0 gm.	Red Venous Ice Blood	Blue Venous Blood	Cytochrome Therapy
Arterial Blood	19	15.5	15.5	15.0	14.8
Venous Blood	12 to 14	10.5	14.2	12.0	8.3
Arteriovenous Oxygen Difference	5 to 7	5.0	1.3	3.0	6.5

normal (0 per cent), which indicated an increased consumption of oxygen. The content of acid-soluble organic phosphates in the serum rose from 0.6 to 1.1 mg. per hundred cubic centimeters; this suggested an increase in available stored phosphate bond energy. The carbon dioxide-combining power was now 51 and 58 volumes per cent. Determinations of urobilinogen by Watson's two hour method gave 1.3, 1.8 and 0.9 Ehrlich units per hundred cubic centimeters. Porphyrinuria continued to be absent. The urinary findings were now normal.

The venous blood, the color of which had previously varied from red to a purplish blue, now varied from blue to a deep blue-black. No bright blood was now seen, though the patient was bled hundreds of times. Venous blood oxygen levels were 6.0, 10.6, 8.3 and 3.8 volumes per cent and arterial levels 16.2, 14.8 and 14.1 volumes per cent. The venous blood on days when the low values were recorded was a deep blue-black in appearance, a phenomenon as striking as was the bright red blood originally noted. Representative readings are recorded in the accompany-

7. Griffith, J. Q., Jr.; Couch, J. F., and Lindauer, M. A.: Effect of Rutin on Increased Capillary Fragility in Man, Proc. Soc. Exper. Biol. & Med. **55**:228 (March) 1944.

ing table. In column 1 we have indicated the normal arterial and venous oxygen volumes, with the normal difference. In column 2 are the normal values for the hemoglobin level in our patient. It will be noted that in anemias of other than severe grade a physiologic adjustment is reached in which a normal arteriovenous oxygen difference is obtained by increased reduction of the oxygen content of the venous blood. In severe anemias, of course, this adaptive mechanism proves inadequate and further compensatory changes in the form of increased cardiac output and circulation rate occur, bringing about an increased number of round trips per red cell. In the third and fourth columns are listed representative values before cytochrome therapy at times when the venous blood was found to be red and when it was blue. It will be seen that both represent anoxic levels of the arteriovenous oxygen difference and that the color change, the intermittency of which seemed at first inexplicable, actually reflected only a change in degree of the constantly present anoxia. Column 5 lists representative levels during cytochrome therapy. Values during therapy proved always within the normal range of arteriovenous oxygen difference, though there was wide variation within that range.

The figures given in columns 1 and 2 are taken from current physiology texts. A recent study[8] derived lower figures, giving a normal arteriovenous oxygen difference of 4.0 and a normal range of 3.1 to 6.1 volumes per cent. In anemic patients with hemoglobin values between 7 and 13 Gm. the arteriovenous oxygen difference averaged 3.8 volumes per cent, while in those with values of less than 7 Gm. of hemoglobin it averaged 2.6 volumes per cent.[9] These studies were made on mixed venous blood obtained by right atrial catheterization, and arterial blood values were either determined on femoral arterial blood or calculated from hemoglobin values. The figures were obtained under basal conditions, whereas ours were not. It is to be expected that the basal state would result in lower values for the arteriovenous oxygen difference, since the percentage of utilization of available oxygen by the tissues rises with exercise. The blood in our case was obtained by puncture from antecubital veins and from radial arteries.

It is to be noted that our patient's low arteriovenous oxygen differences prior to cytochrome therapy were due to inadequate extraction of oxygen from the circulating blood and not, as in the severe cases of cirrhosis recorded by Keys and Snell,[10] to inadequate oxygenation of the hemoglobin itself. His arterial blood oxygen was such as would be expected from the hemoglobin levels, determined independently.

There was no change in the patient's red blood cell count or hemoglobin value during cytochrome therapy. The white blood cell count increased slightly to an average of 7,500 from the 6,500 noted previously, with a normal differential count. On January 29, after two months of therapy, the first rise in eosinophils was recorded at 16 per cent. This gradually increased to 46 per cent by March 5. This finding was accompanied with no other observable allergic manifestations with the possible exception of what may have been a transient hemolytic reaction, manifested by a drop in the red cell count and in the hemoglobin level for a period of

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8. Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by Technique of Right Atrial Catheterization: Normal Values with Observations of the Effect of Anxiety and Tilting, J. Clin. Investigation **24**:326 (May) 1945.

9. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia as Measured by the Technic of Right Atrial Catheterization, J. Clin. Investigation **24**:332 (May) 1945.

10. Keys, A., and Snell, A. M.: Respiratory Properties of the Arterial Blood in Normal Man and in Patients with Disease of the Liver: Position of the Oxygen Dissociation Curve, J. Clin. Investigation **17**:59 (Jan.) 1938.

approximately one week; these reverted to normal (for the patient) despite continuation of therapy. When the eosinophilia reached the high level, however, we discontinued the use of cytochrome, with intent to substitute cytochrome of beef rather than that of equine origin. Administration of cytochrome c was discontinued on March 20 and the eosinophil count began at once to drop, being 32 per cent on March 24, 10 per cent on April 2, 6 per cent on April 7 and 2 per cent on April 16. Other medication was continued.

We attempted to use the interim period to reestablish a base line in the absence of cytochrome therapy. Clinically, the patient reverted within a few days to helpless invalidism. Oozing from the gums reappeared despite the continuance of the use of rutin. Edema of the ankles reappeared. The patient ceased speaking aloud. Tube feeding was required for the first time, and breathing became stertorous. Tremor and cogwheel rigidity did not reappear. Aspiration pneumonia involving the base of the left lung occurred, with a rise in the white blood cell count to 15,700. Erythema of the palms of both hands ("liver palms") appeared during penicillin therapy for the pneumonia and it persisted after administration of the drug had been discontinued. The basal metabolic rate fell to —13 per cent. The serum organic acid-soluble phosphorus fraction on April 9 had fallen to 0.8 mg. per hundred cubic centimeters. The blood lactic acid was 24 mg. per hundred cubic centimeters. The cephalin flocculation remained at 4 plus in twenty-four hours, and the icteric index was 13. Bleeding times were three seconds and one second, clotting times were five and five seconds and clot retraction was complete in two and in three hours. Venous blood oxygen levels were 7.5, 13.7, 11.8, 10.7 and 9.8 volumes per cent; the blood became again intermittently bright red.

Since we were afraid that death would occur from choking or from aspiration pneumonia, further attempts to reach a base line were given up. Administration of beef cytochrome c 150 mg. daily intramuscularly was instituted on April 10, three weeks after discontinuance of the equine cytochrome. The patient continued to deteriorate despite this therapy. His venous blood became bright red and remained so and showed constantly high oxygen levels. The red blood cell count and the hemoglobin level did not change, but studies of smears of the peripheral blood revealed myelocytes, many atypical lymphocytes, poikilocytosis and some anisocytosis and basophilia of the red cells. The platelets numbered 170,000. The prothrombin time was moderately prolonged. Respiratory failure developed, and the patient died in coma on April 24.

Postmortem Examination.—Gross examination was performed two hours after death by Dr. Manuel G. Gichner. The body was that of a slender white man, approximately 150 pounds (68 Kg.) in weight and 6 feet 1 inch (185 cm.) in height. The skin over the entire body was of a bronze color, with more distinct dark brown pigmentation of the lower part of the legs and of the ankles which faded over the toes and the plantar surfaces of the feet. There was slight edema of both ankles, and the left thigh and calf ranged up to 2½ inches (6 cm.) greater in circumference than the right. The fingers and toes were moderately clubbed and cyanotic. There was a small penile scar. No lymphadenopathy was found. The subcutaneous fat and muscle were thin.

The heart weighed 338 Gm., with pallor and slight flaccidity of the muscle. The left lung weighed 550 Gm. and the right 390 Gm. Both were rather firm at the bases, and on the left an area of frankly gray consolidation 10 cm. in diameter was seen.

The strikingly nodular liver appeared small in situ and weighed 1,420 Gm. On cut section, the nodules varied from 0.5 to 2 cm. in diameter. They were dark yellow, with occasional hemorrhagic areas. The septums between the modules were broad and firm. The gallbladder and the extrahepatic biliary channels were un-

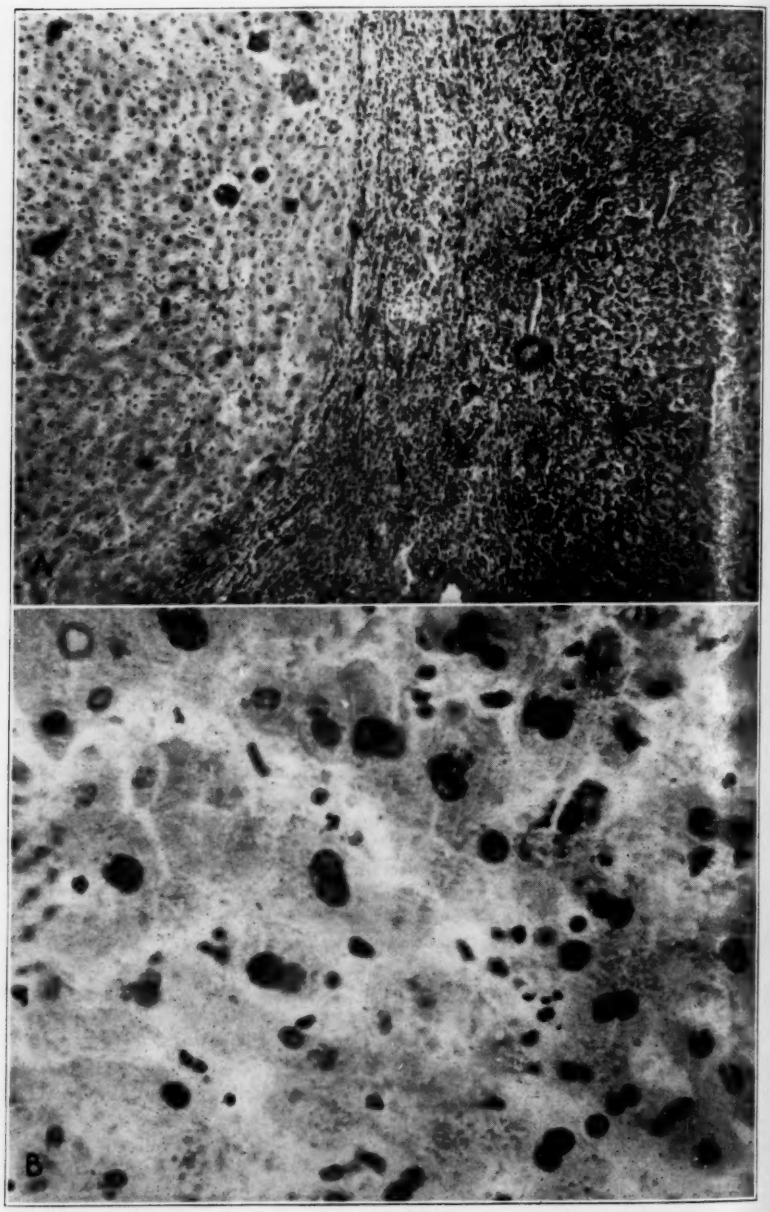

Fig. 2.—Section of the liver. *A*, low magnification, showing adjacent zones of hepatic regeneration, fibrosis with round cell infiltration and hyperplasia of biliary ducts; *B*, high magnification, showing active regeneration of hepatic cells. Note the numerous double-nucleated cells.

changed. The spleen weighed 400 Gm.; its capsule was moderately thickened and wrinkled. Its cut surface had a dull hemorrhagic appearance, with indistinct malpighian corpuscles. The pulp did not scrape readily.

The brain weighed 1,420 Gm. The meninges and the vessels were not visibly altered. In the region of the lenticular nucleus multiple small cavities and softening, with light brown discoloration, were observed. This change, particularly notable in the area of the putamen, extended with diminishnig intensity into the adjacent external capsule posteriorly and the internal capsule anteriorly. No gross

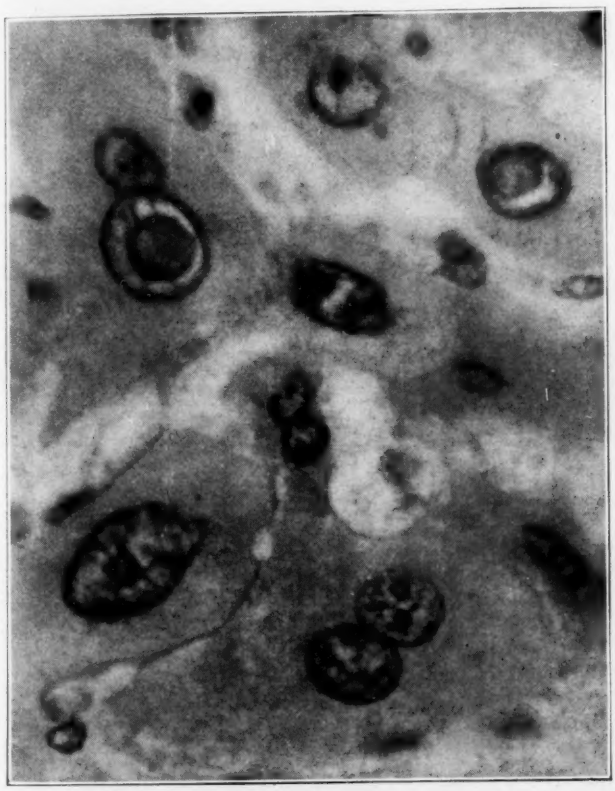

Fig. 3.—Section of the liver, high magnification, showing huge hepatic cells, with cytoplasmic vacuolation and nuclear inclusion particles.

lesions were found in the remainder of the brain or in the upper part of the spinal cord.

The marrow at the junction of the upper and middle thirds of the femur appeared red and hyperplastic, in striking contrast to the usual fatty appearance of marrow in this region.

No changes of significance were noted in the thyroid, adrenals, pancreas, intestinal and urinary tracts, testes or prostate.

Microscopic Examination.—This was performed by Dr. Tom R. Hamilton and Dr. Elizabeth U. Corbell. Tissues were fixed in formaldehyde and stained with

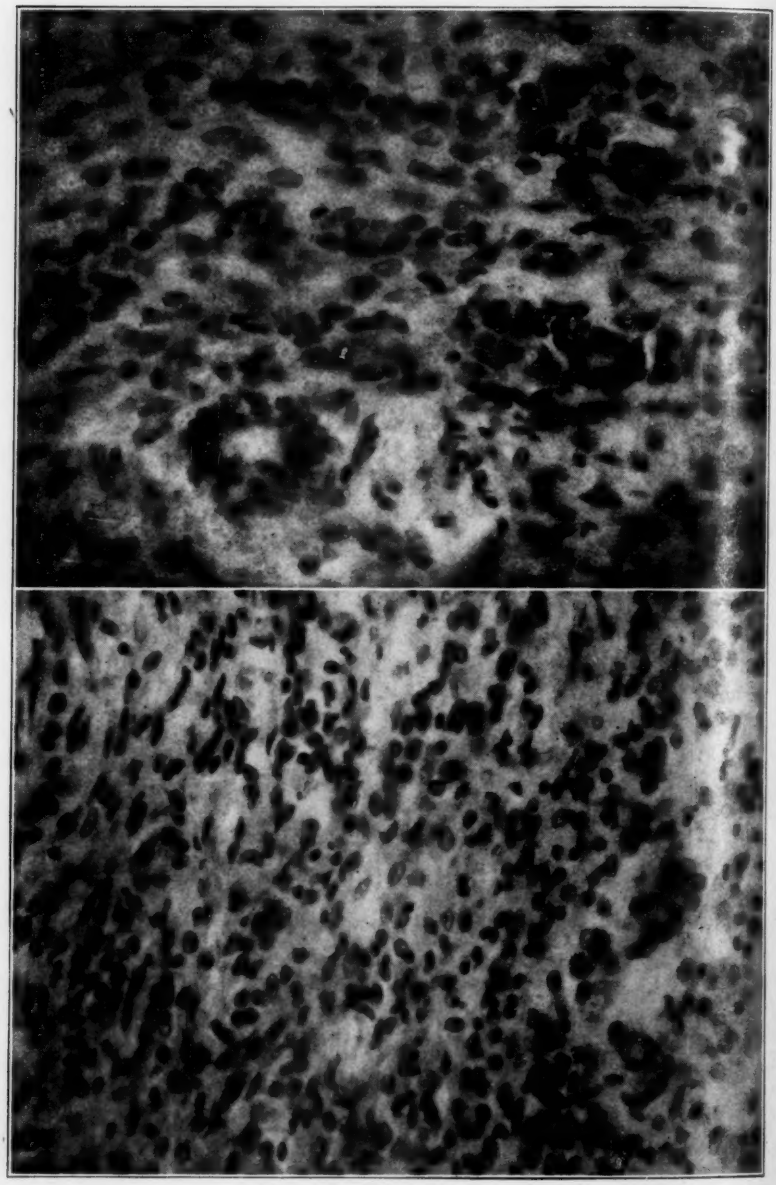

Fig. 4.—Section of the liver. *A*, high magnification, showing hyperplasia of the biliary duct cells; *B*, high magnification, showing nearly adenomatous appearance of hyperplasia of the biliary duct cells.

hematoxylin and eosin. Some sections were stained for fat, glycogen, iron and ceroid.

In sections of the heart, localized vacuolization of the myocardium was noted, especially in the subendocardial region. The myofibrillae and the cross striations of the muscle were somewhat obscure.

The pulmonary sections appeared highly cellular, with polymorphonuclear leukocytes packing the alveolar spaces. Scattered through this exudate were many large pale cells loaded with fat globules as well as numerous pigment-laden macrophages. Some fields were particularly hemorrhagic. Pus cells were found within some of the bronchi. Emphysema predominated in many areas and collapse of the alveoli in others.

The normal lobulation of the liver was lost, and broad zones of dense fibrous tissue coursed through the parenchyma. Numerous small round cells and a few degenerated polymorphonuclear leukocytes were seen in the fibrosed portal spaces. Proliferation of bile ducts was pronounced throughout and suggested an adenomatous process in some areas. In the intervening hepatic nodules there was a remarkable variation in configuration of the cells. Many of the hepatic cells were larger than normal, and a high percentage of them had two or more nuclei. Some of the double and many of the single nuclei were pale, visicular and four and five times the normal size, while other hyperchromatic, bizarre forms were as much as ten times the normal size. Numerous vacuolated hepatic cells were seen, and small discrete granules appeared in some of the vacuoles. Acidophilic inclusion particles were seen in a few of the large vesicular nuclei. These did not stain with glycogen stains. Nearly all the hepatic cells contained fine fat droplets.

In the spleen cellular fibrous tissue appeared prominent in the pulp, and some swelling of cells lining the sinusoids was observed. The sinusoids contained a moderate number of large round cells and granulocytes.

Cloudy swelling and some tubular necrosis were seen in the kidney. Congestion was prominent. Some thickening of vascular walls was noted in small vessels including capillaries of the glomerular tufts.

Decided reticuloendothelial hyperplasia was noted in the lymph nodes. Hematopoiesis, particularly erythopoiesis, encroaching on fatty marrow was prominent in sections from the femur.

Arrest of spermatogenesis was apparent in the testis, and the interstitial cells of Leydig were less conspicuous than usual. There was a slight increase in connective tissue between the seminiferous tubules, and there was some apparent increase in pigment in the interstitial cells.

In the region of the putamen and the adjacent internal and external capsules the brain tissue had a loose, spongy appearance. Numerous small round cells and gitter cells were seen in the spaces. Moderate glial proliferation was present. The walls of the blood vessels in these areas were thickened. Occasional endothelial cells were vacuolated, and some contained acidophilic nuclear inclusion particles. In other sections of the brain, including the cortex, the perivascular spaces contained rather large quantities of fine golden yellow pigment granules both intracellularly and extracellularly. These deposits were usually found in association with slight perivascular accumulations of small round cells. They did not reveal iron when stained.

The skin and the skeletal muscle showed little significant change, except that the cross striations of the muscle fibers were less prominent than in the biopsy specimens.

The pigment granules and globules described in perivascular tissue in the brain and in the interstitial tissue of the testis were acid fast and were assumed to be ceroid. Other tissues stained by the Ziehl-Neelsen technic and shown to contain

ceroid were adrenal cortical cells, regenerating hepatic cells and occasional Kupffer cells of the liver. Ceroid was not found in striated muscle, lung, pancreas, spleen, lymph node, bone marrow or thyroid.

Diagnosis.—The diagnosis was (1) hepatolenticular degeneration, characterized by (*a*) periportal or toxic cirrhosis, with chronic hepatitis and multilobular regeneration (bile ducts and hepatic cords), and (*b*) degeneration in the region of the lenticulostriate nuclei; (2) slight degeneration, hydropic and fatty, of the heart and the liver; (3) parenchymatous degeneration and tubular necrosis of the kidneys; (4) slight fibrosis of the spleen; (5) hyperplasia of the bone marrow of the femur, and (6) bilateral lipoid pneumonia.

COMMENT

Certain pathologic changes referable to anoxia were observed, but they did not seem marked; therapy with cytochrome c may have influenced these processes. Vacuolization in the liver and heart muscle was similar to that observed in various types of anoxia, such as high altitude anoxia,[11] severe anemia [12] and experimentally produced low oxygen tensions.[13] The hyperplastic bone marrow is interpreted as a compensatory response to anoxia, although the effect of cytochrome c therapy is undetermined. Hepatic regeneration was of remarkable degree and is of interest in view of Drabkin's recent report of increased hepatic regeneration in partially hepatectomized rats given injections of cytochrome c.[14] Ceroid pigment, typically found in experimentally induced vitamin E deficiency and dietary cirrhosis in rats, has only recently been observed in human beings.[15]

SUMMARY

A case of hepatolenticular degeneration is described which presented certain unusual features believed to indicate tissue anoxia. Treatment with cytochrome c resulted in reversal of these features and in clinical improvement. Fatal relapse occurred when administration of cytochrome c was discontinued because of development of eosinophilia; terminal reinstitution of cytochrome therapy proved ineffective. Autopsy revealed a remarkable degree of hepatic regeneration and other unusual findings.

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11. Kritzler, R. A.: Acute High Altitude Anoxia: Gross and Microscopic Observations in Twenty-Seven Cases, War Medicine **6**:369 (Dec.) 1944.

12. An evaluation of the vacuolization in anemic anoxia with reference to hydropic as well as fatty change is in progress and unpublished (T. R. Hamilton and G. Chaney).

13. Trowell, O. A.: The Experimental Production of Watery Vacuolation of the Liver, J. Physiol. **105**:268 (Dec. 6) 1946.

14. Drabkin, D. L.: Liver Regeneration and Cytochrome C Metabolism: Influence of Anoxia and of Injection of Cytochrome C, J. Biol. Chem. **171**:409 (Nov.) 1947.

15. Pappenheimer, A. M., and Victor, J.: "Ceroid" Pigment in Human Tissues, Am. J. Path. **22**:395 (March) 1946.

DISREGARDED SEEDBED OF THE TUBERCLE BACILLUS

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THE steady decline in the mortality from tuberculosis has been interpreted as indicating that this disease would in the near future become one of minor significance. This implies that there is a definite ratio, such as was found in the Framingham study,[1] between new cases of tuberculosis and deaths from the disease. Robins[2] pointed out that prior to 1934 there had been no systematic effort made to determine the prevalence of tuberculosis in any large city in the United States and that in surveys made in New York City since 1934 the racial prevlaence of the disease has been found to be completely in discordance with the results anticipated from the application of standards based on mortality statistics. His study indicates that the mortality rate and the annual incidence rate are independent of each other and that the prevalence of clinically active tuberculosis is the resultant of the two. Robins[2] and Fellows[3] determined that the number of adults with clinically active tuberculosis annually was between 2 and 3 per 1,000. Robins[2] and Reid[4] were able to determine the "source case" for only a small percentage of these new cases. The unknown source of infection makes the control of tuberculosis the difficult problem that it is. The present study was undertaken to determine the location and the extent of the unknown source of infection, the disregarded part of Greenwood's[5] "seedbed" of the tubercle bacillus.

From the Laboratories of Pathology, Bellevue Hospital.

Sponsored by the Hegeman Memorial Fund.

1. Final Summary Report, Framingham Monograph 10, July 1924.

2. Robins, A. B.: The Development of Tuberculosis in the Apparently Healthy Adult, Am. Rev. Tuberc. **47**:1, 1943.

3. Fellows, H. H.: Serial Chest Roentgenograms of 3,179 Office Employees, 1926-1938, J. Indust. Hyg. & Toxicol. **22**:157, 1940.

4. Reid, A. C., in discussion on Robins.[2]

5. Greenwood: Epidemics and Crowd-Diseases: An Introduction to the Study of Epidemiology, London, Williams & Norgate, Ltd., 1935.

Routine necropsy protocols contain much information on tuberculosis that is not utilized. In records of this type data relative to the incidence of infection are unreliable, for rarely is sufficient search made for minute tuberculous foci. The major manifestations of tuberculosis as a primary cause of death are well documented. Information relative to caseous foci several millimeters in diameter and to cavity formation is reliable. It is pathologic changes of this type, present in the tissues of persons who died from other diseases, that represent unhealed and often unrecognized tuberculosis from which tubercle bacilli are frequently discharged. The authors regard the caseous focus in the lung as an area of necrotic tuberculous pneumonitis which when it softens and is extruded serves as the source from which tubercle bacilli may be scattered within the lung and to the outside world.

To determine the incidence of deaths from tuberculosis and of unhealed tuberculosis in persons who died from other diseases the necropsy records of Bellevue Hospital on adult patients over 15 years of age have been examined for a ten year period, i.e., 1935 through 1944. Bellevue Hospital was chosen because it is a large public general hospital that is used for teaching purposes by three medical schools. In addition to the usual services in a general hospital, there are a large psychiatric service and a service for the treatment of disease of the chest. To the latter are referred patients with all types of chronic pulmonary conditions. This service acts as a clearing house for tuberculous patients whose residency in the hospital averages about one month.[6] Three fourths of the deaths from tuberculosis on this service occur within one month after the patients' admission to the hospital. A small percentage of the patients with known tuberculosis are cared for by other special services. There is a large necropsy service, with a considerable volume of data available on persons who died from tuberculosis and from various other diseases.

PRESENTATION OF DATA

The data obtained from the necropsy protocols are analyzed in relation to age, sex, race, the presence or absence of caseous foci or of cavity formation in the lung, generalized miliary tuberculosis, tuberculosis as a primary cause of death or as an incidental finding in persons who died from other diseases and the clinical diagnosis relative to the recognition of the tuberculosis found at necropsy.

Table 1.—In table 1 is presented the incidence of unhealed tuberculosis for the necropsy series as a whole. Proportionately there were more male patients with tuberculosis, except in regard to persons under

6. Tuberculosis Reference Statistical Year-Book, New York Tuberculosis and Health Association, 1946.

TABLE 1.—*Unhealed Tuberculosis Seen in Necropsies on Adults Over Fifteen Years of Age According to Race, Sex and Age (Bellevue Hospital 1935 to 1944)*

RACE	SEX	AGE														
		All Patients			15 to 29			30 to 49			50 to 69			Over 70		
		All Patients	Tuberculosis	%	All Patients	Tuberculosis	%	All Patients	Tuberculosis	%	All Patients	Tuberculosis	%	All Patients	Tuberculosis	%
All Patients	Total	7,625	1,041	13.7	417	148	35.4	1,906	384	20.1	3,711	409	11.0	1,591	100	6.2
	Male	5,423	829	15.4	200	69	34.5	1,304	317	24.3	2,828	360	12.7	1,091	82	7.5
	Female	2,202	212	9.6	217	79	36.3	602	67	11.1	883	49	5.5	500	18	3.6
White	Total	6,688	797	12.2	236	76	32.2	1,520	274	18.0	3,409	359	10.5	1,523	88	5.9
	Male	4,859	660	13.7	113	38	33.6	1,073	229	21.3	2,612	317	12.2	1,061	76	7.1
	Female	1,829	137	7.3	123	38	30.9	447	45	10.0	797	42	5.3	462	12	2.6
Colored	Total	937	244	25.8	181	72	39.8	386	110	28.5	302	50	16.5	68	12	17.6
	Male	565	169	29.3	88	32	36.3	231	88	18.1	216	43	19.9	30	6	20.0
	Female	372	75	20.8	93	40	43.0	155	22	14.2	86	7	8.1	38	6	13.6

TABLE 2.—*Necropsies on Adults with Unhealed Tuberculosis Showing Nontuberculous and Tuberculous Deaths in Relation to Types of Pulmonary Lesion, Race and Age (Bellevue Hospital 1935 to 1944)*

Type of Pulmonary Lesion	Race	AGE																			
		All Ages				15 to 29				30 to 49				50 to 69				Over 70			
		Total	Death		%	Total	Death		%	Total	Death		%	Total	Death		%	Total	Death		%
			Non-tuberculous	Tuberculous	Tuberculous		Non-tuberculous	Tuberculous	Tuberculous		Non-tuberculous	Tuberculous	Tuberculous		Non-tuberculous	Tuberculous	Tuberculous		Non-tuberculous	Tuberculous	Tuberculous
All Patients	Total	1,041	248	793	76.2	148	0	148	100.0	384	52	332	86.5	410	147	263	64.2	99	49	50	50.5
	White	797	230	567	71.2	76	0	76	100.0	274	47	227	82.9	359	136	223	62.2	88	47	41	46.6
	Negro	244	18	226	92.7	72	0	72	100.0	110	25	105	95.5	51	11	40	78.5	11	2	9	81.9
Cavity	Total	793	131	662	83.6	113	0	113	100.0	315	26	289	91.8	298	78	220	73.9	67	27	40	59.7
	White	618	121	497	80.5	71	0	71	100.0	229	3	206	90.0	260	72	188	72.4	58	26	32	55.2
	Negro	175	10	165	94.4	42	0	42	100.0	86	3	83	96.5	38	6	32	84.2	9	1	8	88.9
Caseous focus	Total	152	104	48	31.8	8	0	8	100.0	45	24	21	46.7	77	62	15	19.5	22	18	4	18.2
	White	130	100	30	23.1	1	0	1	100.0	35	23	12	34.3	72	59	13	18.1	22	18	4	18.2
	Negro	22	4	18	81.1	7	0	7	100.0	10	1	9	90.0	5	3	2	40.0	..	..	..	....
No cavity or caseous focus	Total	96	13	83	86.5	27	0	27	100.0	24	2	22	91.7	35	7	28	80.0	10	4	6	60.0
	White	49	9	40	81.7	4	0	4	100.0	10	1	9	90.0	27	5	22	81.5	8	3	5	62.5
	Negro	47	4	43	91.9	23	0	23	100.0	14	1	13	92.9	8	2	6	75.0	2	1	1	50.0

30 years of age, and more Negroes than white patients. Unhealed tuberculosis is recorded for both sexes, for both races and for all age groups.

Table 2.—The cases of unhealed tuberculosis are analyzed in table 2. In most cases in which tuberculosis was recorded in the necropsy records of Negroes it was the primary cause of death, whereas 29 per cent of the white patients died from diseases other than tuberculosis. This suggests that if a progressive tuberculosis becomes established in Negroes they seldom survive long enough to die from other causes, in contrast to the occurrence among the white race. It does not indicate, however, that persons of the Negro race once infected cannot prevent the infection from progressing. Formation of tuberculous cavities in the lungs of patients who died from disease other than tuberculosis was more frequently noted in persons of the white race.

Caseous foci without cavity formation in the lungs were more frequently mentioned in reports on white patients and were more often an incidental finding. The caseous foci recorded were all at least 5 mm. in diameter, and undoubtedly many smaller foci of this type would have been noted had a greater awareness of their significance been present. That the caseous focus is not an innocuous lesion is shown by the fact that when this lesion was found without cavity formation in the lungs it was associated with death from tuberculosis in 23 per cent of the white patients and in 81 per cent of the Negroes.

Neither cavity formation nor caseous focus in the lungs was recorded in 9.2 per cent of the patients. The number of white patients for which neither was recorded was 6 per cent and the number of Negroes 19 per cent. The greater percentage among the Negroes, with one half of them being under 30 years of age, suggests that small caseous foci in the lungs had been overlooked. This explanation may or may not apply to the white patients since 90 per cent of these were in the older age group. In this group 86.5 per cent died from tuberculosis.

The relation of age to unhealed tuberculosis and to death from this disease is significant. Tuberculosis was the cause of death in all patients under 30 years for whom unhealed tuberculous lesions were recorded but in only one half of the patients over 70 years of age. The latter condition was much more frequent among the white patients.

Table 3.—The relation of generalized miliary tuberculosis to the type of pulmonary lesions, to race and to age is presented in table 3. Generalized miliary tuberculosis was present in 18.9 per cent of the patients who died from tuberculosis. It was twice as frequent among Negroes as among white persons. It was recorded least often among patients with cavity formation in the lungs. When caseous foci only were recorded and when neither cavity formation nor caseous foci were present in the lungs there was a high frequency of generalized miliary

TABLE 3.—*Generalized Miliary Tuberculosis in Relation to Type of Pulmonary Lesion, Race and Specified Age Groups (Bellevue Hospital 1935 to 1944)*

AGE

TABLE 3.—*Generalized Miliary Tuberculosis in Relation to Type of Pulmonary Lesion, Race and Specified Age Groups (Bellevue Hospital 1935 to 1944)*

Type of Pulmonary Lesion	Race	AGE											
		All Ages			15 to 29			30 to 49			50+		
		Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis	Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis	Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis	Tuberculous Deaths	Miliary Tuberculosis	Percentage with Miliary Tuberculosis
All Patients	Total	793	150	18.9	148	35	23.6	332	58	17.4	313	57	18.2
	White	567	83	14.6	76	10	13.1	227	31	13.6	264	42	15.9
	Negro	226	67	29.6	72	25	34.7	105	27	25.7	49	15	30.6
Cavity	Total	662	61	9.2	113	11	9.7	289	26	9.0	260	24	9.1
	White	497	39	7.8	71	7	9.8	206	16	7.7	220	16	7.2
	Negro	165	22	13.3	42	4	9.5	83	10	12.0	40	8	20.0
Caseous focus	Total	48	23	47.9	8	7	87.5	21	11	52.4	19	5	23.3
	White	30	13	43.3	1	1	100.0	12	7	58.3	17	5	29.4
	Negro	18	10	55.5	7	6	85.7	9	4	44.4	2	0	....
No cavity or caseous focus	Total	83	66	79.5	27	17	62.9	22	21	95.4	34	28	82.3
	White	40	31	77.5	4	2	50	9	8	88.8	27	21	77.8
	Negro	43	35	81.4	23	15	65.2	13	13	100.0	7	7	100.0

TABLE 4.—*Data on Patients Who Died With Unhealed Tuberculosis (Bellevue Hospital 1935 to 1944)*

Cause of Death	Type of Tuberculous Lesion in Lung	AGE														
		All Ages			15 to 29			30 to 49			50 to 69			Over 70		
		No.	Diagnosed Clinically	%	No.	Diagnosed Clinically	%	No.	Diagnosed Clinically	%	No.	Diagnosed Clinically	%	No.	Diagnosed Clinically	%
Tuberculosis	Total	793	703	88.7	148	143	96.7	332	308	92.8	263	222	84.5	50	30	60.0
	Cavity	662	613	92.6	113	113	100.0	289	278	96.2	220	194	88.2	40	28	70.0
	Caseous focus	48	27	56.3	8	5	62.5	21	14	66.7	15	8	53.3	4	0	0
	No cavity or caseous focus	83	63	75.6	27	25	92.6	22	16	72.8	28	20	71.4	6	2	33.3
Other disease	Total	248	66	26.7	..	..	..	52	20	38.5	147	38	25.9	49	7	14.3
	Cavity	131	53	41.5	..	..	..	26	13	50.0	78	33	42.3	27	7	25.9
	Caseous focus	104	12	11.6	..	..	..	24	7	29.2	62	5	8.1	18	0	0
	No cavity or caseous focus	13	0	0	..	..	..	2	0	0	7	0	0	4	0	0

tuberculosis. In cases of this type it is often difficult to determine the original source from which the dissemination occurred.

The group of 150 patients with generalized miliary tuberculosis was composed of 100 males and 50 females. Proportionately, there was no difference between males and females in either race in regard to the group under 30 years of age, but in the groups over 30 years of age in both races generalized miliary tuberculosis was observed twice as frequently among females as among males. The most frequent occurrence of generalized miliary tuberculosis was in the group under 30 years of age, with the second greatest frequency being found in the group over 50 years of age.

Table 4.—The clinical records of all patients with unhealed tuberculosis observed at necropsy were examined to determine whether this disease had been mentioned in the clinical diagnosis. Failure to find tuberculosis listed was interpreted as meaning either that the disease had not been suspected or that if considered it had been relegated to a place of no importance. The principal point of interest in table 4 is the correlation of the clinical diagnosis with the findings at necropsy.

Tuberculosis was diagnosed clinically in 89 per cent of the cases in which it was the primary cause of death. It was diagnosed for 96.7 per cent of the persons under 30 years of age and for 60 per cent of the patients over 70 years of age. It was diagnosed also in but 70 per cent of the patients over 70 years of age who had tuberculosis cavity formation in the lungs. There was a decrease in the diagnosis of tuberculosis with the increase of the age of the patient.

Unhealed tuberculosis present in those who died from other diseases received little clinical attention, for in less than half of the patients with tuberculous cavity formation in the lungs was a clinical diagnosis of tuberculosis recorded.

Perhaps the data from the necropsy series may not be applicable to the problem of tuberculosis in a large community. Nevertheless it seemed worth while to compare these data with those contained in the death registry [7] of the city as a whole for the same period.

Table 5.—The patients on whom necropsy was performed at Bellevue Hospital equaled 1 per cent of the white persons and 1.7 per cent of the Negroes over 15 years of age who died in New York city. The data presented in table 5 show that the necropsy series contains a higher proportion of white males and of Negroes of both sexes than the series represented in the city registry. Although there is the same general trend relative to age distribution in the two series, the necropsy series contains a lower proportion of patients over 70 years of age.

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7. The data for the New York city deaths were kindly supplied by the Bureau of Records and Statistics, Department of Health, New York City.

TABLE 5.—*Total Adult Deaths in New York City Registry Compared With All Necropsies on Adults at the Bellevue Hospital According to Age, Race and Sex (1935 to 1944)*

Race and Sex	AGE									
	All Ages		15 to 29		30 to 49		50 to 69		Over 70	
	Total	%	Total	%	Total	%	Total	%	Total	%
	All Deaths — New York City Death Registry									
Total	717,943	100.0	35,098	4.8	138,276	19.2	331,198	46.1	213,370	29.9
White Male	367,946 (51.2%)	100.0	14,018	3.8	69,701	18.9	186,872	50.7	97,355	26.6
White Female	297,198 (41.4%)	100.0	13,291	4.4	47,463	16.3	126,102	42.4	110,342	36.9
Negro Male	27,845 (3.9%)	100.0	3,461	12.4	12,008	43.1	10,006	35.9	2,370	8.6
Negro Female	24,954 (3.5%)	100.0	4,328	17.5	9,104	36.4	8,218	32.9	3,304	13.2
	All Necropsies — Bellevue Hospital									
Total	7,625	100.0	417	5.4	1,906	26.3	3,711	48.5	1,591	19.8
White Male	4,859 (63.7%)	100.0	113	2.3	1,073	22.0	2,612	53.7	1,061	22.0
White Female	1,829 (23.9%)	100.0	123	6.7	447	24.4	797	43.6	462	25.3
Negro Male	565 (7.4%)	100.0	88	15.4	231	40.9	216	38.2	30	5.5
Negro Female	372 (5.0%)	100.0	93	25.0	155	41.6	86	23.1	38	11.3

TABLE 6.—*Tuberculosis as a Primary Cause of Death*

Race and Sex	All Ages		AGE							
			15 to 29		30 to 49		50 to 69		Over 70	
	Total	%	Total	%	Total	%	Total	%	Total	%
			New York City Death Registry							
Total	37,425	100.0	8,786	23.4	15,569	41.6	11,194	29.9	1,876	5.1
White Male	19,281 (51.5%)	100.0	2,182	11.3	7,992	41.4	7,910	41.0	1,197	6.3
White Female	8,528 (22.8%)	100.0	2,908	34.1	3,180	37.2	1,874	21.9	561	6.8
Negro Male	5,618 (15.0%)	100.0	1,546	27.5	2,929	52.1	1,069	19.0	74	1.4
Negro Female	3,998 (10.7%)	100.0	2,151	53.8	1,463	36.7	341	8.5	38	1.0
			Bellevue Hospital Necropsies							
Total	793	100.0	148	18.6	332	41.8	263	33.1	50	6.5
White Male	461 (58.1%)	100.0	38	8.2	192	41.6	197	42.7	34	7.5
White Female	106 (13.3%)	100.0	38	35.8	35	33.0	26	24.5	7	6.7
Negro Male	158 (19.9%)	100.0	32	20.2	85	53.8	35	22.1	6	3.9
Negro Female	68 (8.7%)	100.0	40	58.8	20	29.4	5	7.3	3	4.5

TABLE 7.—*Percentage of Tuberculous Deaths in Specified Age Groups*

Race and Sex	AGE														
	All Ages			15 to 29			30 to 49			50 to 69			Over 70		
	Total	Tuberculous Deaths	%	Total	Tuberculous Deaths	%	Total	Tuberculous Deaths	%	Total	Tuberculous Deaths	%	Total	Tuberculous Deaths	%
New York City Death Registry															
Total	717,943	37,425	5.2	35,098	8,786	25.0	138,276	15,569	11.2	331,198	11,194	3.4	213,370	1,876	0.8
White Male	367,946	19,281	5.2	14,018	2,182	15.5	69,701	7,992	11.4	186,872	7,910	4.2	97,355	1,197	1.2
White Female	297,198	8,528	2.8	13,291	2,908	21.8	47,463	3,180	6.7	126,102	1,874	1.5	110,342	561	0.5
Negro Male	27,845	5,618	20.1	3,461	1,546	44.6	12,008	2,929	24.4	10,006	1,069	10.6	2,370	74	3.1
Negro Female	24,954	3,998	16.0	4,328	2,151	49.7	9,104	1,468	16.1	8,218	341	4.1	3,304	38	1.1
Bellevue Hospital Necropsies															
Total	7,625	793	10.4	417	148	35.4	1,906	332	17.4	3,711	263	7.0	1,591	50	3.1
White Male	4,859	461	9.5	113	38	33.6	1,076	192	17.8	2,612	197	7.5	1,061	34	3.2
White Female	1,829	106	5.8	123	38	30.9	447	35	7.8	797	26	3.2	462	7	1.5
Negro Male	565	158	27.9	87	32	36.8	231	85	36.7	216	35	16.1	30	6	20.0
Negro Female	372	68	18.2	93	40	43.0	155	20	12.9	86	5	5.8	38	3	7.9

Table 6.—A comparison of deaths from tuberculosis in the two series is presented in table 6. The proportion of males is higher in the necropsy series. There is a higher proportion of the group under 30 years of age represented in the city registry than in the necropsy series. The trend in age distribution is similar in the two series.

Table 7.—The relation of tuberbulous deaths to total deaths in the two series is presented in table 7. Proved tuberculous deaths are twice as frequent in the necropsy series as in the city series. The higher percentages in the necropsy series pertain to all but three categories of patients, i.e., Negroes, male and female, under 30 years of age and Negro women between 30 and 49 years of age. The ratio between the necropsy data and the data from the city registry is 1.4 to 1 for the group under 30 years of age and 3.9 to 1 for the group over 70 years of age. Seventy-six per cent of those in the necropsy series under 30 years of age who died from tuberculosis were from the service for the treatment of disease of the chest while in the group over 70 years of age 68 per cent were from other services. It can hardly be argued that the higher proportion of deaths from tuberculosis in the necropsy series is due solely to the fact that the hospital has a large active service for patients with tuberculosis.

Table 8.—Since there is considerable agreement between the data from the city registry and the necropsy data and since the mortality, from tuberculosis in the city, based on data from the city registry, has shown a considerable decline in the past two decades, it would seem logical to expect to find a similar trend in the necropsy data. In table 8 are presented the necropsy data from Bellevue Hospital for the two periods of 1920 to 1922 and 1940 to 1942. A comparison of the two sets of data shows little change in the incidence of unhealed tuberculosis. Proportionally there were fewer necropsies on persons under 50 years of age in the later period. This same trend has been reported [8] for other necropsy series in the city. It reflects the trend [9] in the aging of the population.

Samples of a single generation are present in both series. Thus the group 15 to 29 years of age in 1920 to 1922 is represented in the group 30 to 49 years of age in 1940 to 1942. Comparisons of the two samples of generations reveal two points of interest. First, as a generation ages the ratio of deaths from other diseases to deaths from tuberculosis increases. Second, there is a decrease in the ratio of deaths from tuber-

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8. Medlar, E. M.: The Incidence of Pathologically Significant Tuberculosis in Routine Necropsies in Private and Public General Hospitals, New York State J. Med. **47**:582, 1947.

9. Dublin, L. I.: Health Problems of an Aging Population, Statist. Bull. Metrop. Life Ins. Co. (no. 12) **27**:6, 1946.

culosis to deaths from other diseases in persons with unhealed tuberculosis. These two phenomena suggest that as a generation ages increments of tuberculosis are added and that the decrease of deaths from the disease may be due to changes in the soil rather than to any change in the pathogenicity of the tubercle bacillus. Examination of the clinical histories of persons of the ages of 40 to 60 years who died from tuberculosis shows that in some but not in all cases tuberculosis had been diagnosed prior to the final illness. Examination of the clinical histories of persons

TABLE 8.—*Comparison of Necropsies at Bellevue Hospital for the Years 1920 to 1922 and 1940 to 1942 Relative to Death from Tuberculosis and to Unhealed Tuberculosis in Patients Who Died from Other Diseases*

Age	Total Deaths	Deaths Due to Tuberculosis	Deaths Due to Other Diseases		Ratio of Deaths Due to Tuberculosis to Deaths Due to Other Diseases Accompanied With Tuberculosis
			Unhealed Tuberculosis Present	No Unhealed Tuberculosis	
(1)	(2)	(3)	(4)	(5)	(6) = (3) and (4)
			1920 to 22		
Total	1,307	191 (14.6%)	83 (6.4%)	1,033 (79.0%)	2.3
15 to 29	173 (13.2%)	45 (26.0%)	2 (1.2%	126 (72.8%)	22.5
30 to 49	507 (38.8%)	106 (20.9%)	29 (5.7%)	372 (73.5%)	3.6
50 to 69	506 (38.8%)	33 (6.5%)	32 (8.3%)	431 (85.2%)	0.8
Over 70	121 (9.2%)	7 (5.7%)	10 (8.2%)	104 (86.1%)	0.7
			1940 to 42		
Total	2,244	282 (12.5%)	152 (6.8%)	1,810 (80.7%	1.8
15 to 29	88 (3.9%)	31 (46.6%)	...	47 (53.4%)	...
30 to 49	528 (23.5%)	110 (20.8%)	35 (6.6%)	383 (72.6%)	3.1
50 to 69	1,159 (51.7%	113 (9.7%)	86 (7.4%)	960 (82.9%)	1.3
Over 70	469 (20.9%)	18 (3.8%)	31 (6.6%)	420 (89.6%)	0.6

TABLE 9.—*Tuberculosis Among Employees of the Metropolitan Life Insurance Company After Employment (Detected Between 1935 and 1946)*

Length of Employment in Years	All Patients		Patients on Whom a Normal Roentgenogram Was Obtained Previously		Patients Previously Examined by Fluoroscopy	
	No.	%	No.	%	No.	%
Total	226	100.0	104	100.0	122	100.0
Less than 1	15	6.6	10	9.6	5	4.1
1 to 5	64	28.3	32	30.8	32	26.2
5 to 10	80	35.5	34	32.7	46	37.7
10 to 15	44	19.4	18	17.3	26	21.3
Over 15	23	10.2	10	9.6	13	10.7

who died from other causes but who harbored unhealed tuberculosis fails to reveal a diagnosis of tuberculosis for any previous illness in the majority of instances. These facts suggest that the tuberculosis observed at necropsy on older persons has not necessarily been carried over from a previous decade.

Table 9.—These observations are confirmed by clinical studies of adults on whom normal roentgenograms of the chest have been obtained or who have shown a negative reaction to tuberculin. In table 9 [10] is presented the new instances of pulmonary tuberculosis found among employees of the Metropolitan Life Insurance Company in relation to the length of service in the company. The persons in this group had either a normal roentgenogram or a normal fluoroscopic reading of the chest prior to their employment. The average age at the time of employment was 20 years. All the persons were subjected to at least a yearly fluoroscopic examination of the chest. Sixty-three per cent of the patients were found to have the disease between the first and the tenth year after employment, but 10 per cent had been employed over fifteen years. The source [11] of the infection could not be traced to anyone in the employment of the company, and the history of contact with a person with known tuberculosis could be elicited in only 10 per cent of the cases. It is our judgment, based on considerable experience at necropsies, that these infections are new ones acquired in adult life rather than "latent" infections too minute to be detected several years previously. This is a graphic illustration of increments of tuberculosis in an adult population that was as free from demonstrable tuberculosis as it is possible to determine from roentgenographic studies of the chest.

SUMMARY OF DATA

Cavity formation or caseous foci in the lungs were present in 90 per cent of the persons with unhealed tuberculosis in the necropsy series. Fifty-six per cent of all patients with cavity formation were under 50 years of age, and death was ascribed to tuberculosis in 93 per cent of this group. However only 71 per cent of those over 50 years of age died from tuberculosis. One sixth of the persons with cavity formation died from other diseases, 80 per cent being over 50 years of age. A clinical diagnosis of tuberculosis was made for 94 per cent of the persons with cavity formation in the group under 50 years of age. A clinical diagnosis was made for 81 per cent of a similar group over 50 years of age when tuberculosis was the cause of death and in only 38 per cent when death was due to other diseases. The latter group represents one seventh of all persons with cavity formation.

The presence of caseous foci without cavity formation in the lungs was recorded in 2 per cent of all necropsies. We regard foci of this type as areas of necrotic tuberculous pneumonitis and as the precursors to cavity formation. Until completely organized they cannot be regarded as "closed" foci and must be considered as a potential source for the

10. The data contained in this table were kindly supplied by Dr. Harold Haynes Fellows, Associate Medical Director of the Metropolitan Life Insurance Company.

11. Fellows, H. H.: Personal communication to the authors.

discharge of tubercle bacilli in the air. One third of the patients with this type were under 50 years of age, 54 per cent of whom died from tuberculosis, and two thirds were over 50 years of age, with death from tuberculosis occurring in only 19 per cent. Of the Negroes, 9 per cent had this type, 77 per cent of these being under 50 years of age; death from tuberculosis occurred in 94 per cent. Of the white patients, one sixth had this type, 72 per cent of these being over 50 years of age; death from tuberculosis occurred in only 18 per cent. If the ratio of patients with caseous foci to those with cavity formation is an acceptable criterion, caseous foci show a greater tendency to soften and excavate in Negroes than in white patients. This may be one reason for the difference in the behavior of the disease in the two races. These caseous foci have not received the attention which they merit, for in only 25 per cent of the cases in which they were described was a clinical diagnosis of tuberculosis made.

While the softening of a necrotic area of tuberculous pneumonitis, with a discharge of the contents through the bronchi, is not a complete protection against massive generalized dissemination of the disease, it seems to be an important factor. Cavity formation in the lungs was present in 83 per cent of the persons who died from tuberculosis, with only 9 per cent having generalized miliary tuberculosis. Of the persons dead from tuberculosis in whom caseous foci were present in the lungs or other tissues, without cavity formation in the lungs, 48 per cent had generalized miliary tuberculosis.

In 40 per cent of the cases involving persons over 50 years of age with unhealed pulmonary tuberculosis this disease was not mentioned in the clinical diagnosis. Of this group, 77 per cent were white males, of whom one half had cavity formation in the lungs. A clinical recognition of the tuberculosis would not have altered the primary clinical diagnosis or the treatment prescribed in the majority of instances. However, failure to recognize the presence of pathologically active tuberculosis precluded steps to lessen the danger of spread of the infection.

If all the persons who died from tuberculosis and all the persons for whom a clinical diagnosis of tuberculosis was made are excluded from the necropsy series, there remain 183 persons (2.5 per cent) with unhealed disease, 40 per cent of whom had cavity formation in the lungs. Expressed in the usual statistical terms, this represents a rate of 1,000 persons with unrecognized cavity formation in the lungs per 100,000 of the population.

The data from the necropsies and those from the city registry agree in most instances as to the age distribution for deaths as a whole and for deaths from tuberculosis. The differences in the two series relative to sex and age are probably due to the composition of the population of

the hospital plus the fact that it is usually easier to obtain permits for necropsy on male patients. Permits for necropsy at Bellevue Hospital are obtained by the resident staff, and success in procuring them rests in no small way on the zeal with which they are sought. Greater effort is exerted to obtain permits for necropsy on patients who had presented difficult diagnostic problems or unusual clinical features. More interest is usually manifested in young adults than in the aged. Whatever selectivity there may be in the necropsy series is due to the clinical interest in the cases and to the ability to obtain permits rather than to the nature of the disease disclosed at necropsy. We believe that the necropsy series represents a fair random sample of deaths in the city. A comparison of the necropsy data and the data from the city registry relative to deaths as a whole in relation to deaths from tuberculosis shows a ratio of 1.4 to 1 in the group under 30 years of age and of 3.9 to 1 in the group over 70 years of age. An impression is gained that the death rate from tuberculosis is too high among Negroes under 30 years of age and is below the actual among all other categories represented in the city registry. This seems plausible, for the causes of death as listed in the city registry are in large part based on the clinical and not on the pathologic diagnosis, and in the city as a whole three fourths of the persons who died were over 50 years of age. Twenty per cent of the patients of this age in the necropsy series who died from tuberculosis had not been recognized clinically as being affected with the disease.

A comparison of the necropsies at Bellevue Hospital for the years 1920 to 1922 and 1940 to 1942 fails to reveal any striking difference in the incidence of unhealed tuberculosis in the two series. A similar comparison of necropsies on young children [8] revealed a decrease of 80 per cent in deaths from tuberculosis between 1920 and 1940. Deaths from tuberculosis at Bellevue Hospital in 1940 to 1942 may not reflect the true situation in New York city, for in recent years a majority of the hospitals have adopted a policy of transferring tuberculous patients to special services as soon as the disease is diagnosed and not a few such transfers are made to Bellevue Hospital. This does not apply to the unhealed tuberculosis present in the groups who died from other diseases, and a comparison of the two series in this respect reveals no significant difference between them. One third of the persons with tuberculosis in the two series were in this group, and the number of these over 50 years of age increased from 63 to 77 per cent between 1920 and 1940. It appears that unrecognized and unhealed tuberculosis is concentrated in the population over 50 years of age; the condition is more often met with among males than among females.

COMMENT

Whenever the problem of tuberculosis is discussed, it is usual to place great emphasis on the decline in the mortality rate. To argue that the continuity of tuberculosis revolves about the mortality rate is to ignore the essential nature of the pathogenesis of the disease. Today a majority of the persons ill with tuberculosis are restored to a state of clinical well-being, and by proper management they may survive for years to die eventually from some other disease. Throughout their life many continue to shed tubercle bacilli, and it is unwise to ignore these persons for they constitute one part of the seedbed.

There are certain other facts which show that tuberculosis is none too well controlled. In the year 1945,[6] 35 per cent of the deaths from tuberculosis in New York city occurred out of hospital and one third of the deaths took place within one month after the patients were admitted to hospital. Twenty-nine per cent of the patients with tuberculosis left the hospital against medical advice. Clinical relapse of the disease accounted for 23 per cent of the admissions to the hospital. Of the newly discovered cases, 12.4 per cent were first known through death registrations. One half of the patients with tuberculosis were discharged either improved or unimproved. These facts relate to the known part of the seedbed.

Unhealed tuberculosis is seldom found recorded in the records of necropsy on adults under 30 years of age if death was due to some other disease. This suggests that if unaltered in its course progressive tuberculosis is a highly lethal disease in young adults. The finding of unhealed tuberculosis in increasing numbers of persons dead from other diseases, in proportion to those dead from tuberculosis, indicates that a progressive tuberculosis acquired in later life tends to be less explosive in type. It is in this part of the population, i.e., persons over 50 years of age, that tuberculosis is less likely to be suspected. This constitutes the unknown part of the seedbed that the necropsy data indicates contains 1,000 persons with cavity formation per 100,000 of the population.

All that is needed to initiate a new case of progressive tuberculosis is for a few tubercle bacilli to lodge in a favorable place in a lung and in a favorable soil. A larger number of new cases might develop in an environment heavily polluted with tubercle bacilli, but it is also possible to have cases occur from a chance exposure to relatively few bacilli. When there are many unrecognized spreaders of bacilli, chance exposure could occur often and new cases could develop without a discernible source of contact. The experience of the Metropolitan Life Insurance Company relative to the development of tuberculosis among its employees after their employment is an excellent example of such a situation. This appears to be the situation also in New York city, where no source of

contact is found for the majority of the newly discovered cases. This situation mitigates against breaking the continuity of the disease.

Frost,[12] in discussing the control of tuberculosis, proposed the thesis that the tubercle bacillus is losing ground because there are fewer deaths from the disease and because "there appears to be no good reason to doubt that the prevalence of open cases is diminishing at something like the same rate as mortality from phthisis." This depends on what is meant by "open" cases. Cases of minimal tuberculosis used to be considered as "closed" cases, but today this is not so. Careful bacteriologic studies have shown that a considerable number of patients with "arrested" tuberculosis and of persons with tuberculosis "of no clinical significance" discharge tubercle bacilli intermittently. Frost probably did not include these patients in his thoughts of the "open" case. It is the survivors who discharge tubercle bacilli more than the persons who die from the disease who enhance the chance for continuity of tuberculosis. A good parasite, for its survival, establishes itself in a large number of hosts, but only a minority succumb to the invasion. In this respect the tubercle bacillus has done well. With the population over 50 years of age being larger today than it was twenty years ago, the necropsy data suggest that the seedbed for the tubercle bacillus has enlarged and that the chances for its survival are enhanced rather than diminished.

The campaign waged to eradicate tuberculosis in cattle in this country struck at the core of the problem, i.e., the eradication of the seedbed. The core of the problem of tuberculosis in man is the same as that in cattle, but the same plan of attack can hardly be recommended.

Control of tuberculosis, meaning a decrease of the continuity of the disease, requires an intelligent supervision of the seedbed to prevent the return to the soil of those factors which favor the tubercle bacillus. This means a planned follow-up of all persons with unhealed disease, which includes those in whose roentgenograms shadows are revealed regardless of whether the disease is considered active or inactive. Thought also must be given to the socioeconomic factors that favor the disease. In addition an intensified search must be made for a cure, in a pathologic as well as in a clinical sense, of those who have a progressive disease.

The problem of the continuity of tuberculosis, as seen at necropsy, appears formidable. This view corroborates the following statement by Greenwood [5]:

> At the worst, looking at the position epidemiologically, we might fear that if a population such as ours were, through the breakdown of the machinery of civilization, again exposed to the environmental conditions of a city slum of the eighteenth

12. Frost, W. H.: How Much Control of Tuberculosis? in Papers of Wade Hampton Frost: A Contribution to Epidemiological Method, New York, The Commonwealth Fund, 1941.

or early nineteenth century, the reaction in terms of tuberculosis mortality would be sharper than in the past.

Without doubt it is idle to speak of the conquest of tuberculosis; tuberculosis has not been and so far as one can see never will be conquered. We may, however, reasonably expect a further decline in mortality, provided that our means allow us to improve the general environmental conditions of the people.

SUMMARY

Among patients who died from tuberculosis the clinical diagnosis was incorrect six times more often for persons over 50 than for persons under 30 years.

Among patients who died from other diseases, but who harbored tuberculosis which was capable of spreading, there was clinical recognition of tuberculosis in only one fourth.

Tuberculosis tends to be less explosive in type in old persons than in young adults. Older persons can have progressive disease with so few manifestations of illness that they may not seek the advice of a physician. In these circumstances they remain unrecognized spreaders of the infection.

The registration of death from tuberculosis in New York city appears to be below the actual with respect to persons over 50 years of age.

In a high proportion of new cases of tuberculosis in adults in New York city the disease is apparently contracted from unrecognized sources of infection.

Mortality rates, encouraging as they seem, do not indicate either the extent or the location of the seedbed in which the tubercle bacillus resides. The seedbed may well be greater in extent today than it was twenty years ago, for it is largely concentrated in persons, principally men, over 45 years of age, and these are more numerous today than they were a generation ago.

The seedbed must be controlled if the continuity of the disease is to be broken. This requires an intensified search for unknown spreaders of the infection, a more thorough follow-up of known cases of tuberculosis, even if considered "of no clinical significance," a more thorough hospitalization of persons with active tuberculous disease, intelligent action on socioeconomic problems to prevent a return of those factors which favor the propagation of the tubercle bacillus and an intensified search for a cure of the disease in a pathologic as well as in a clinical sense.

The seedbed must be eradicated if tuberculosis is to be eradicated.

APICAL SYSTOLIC MURMUR

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IN PREVIOUS reports [1] it has been pointed out that the true significance of the relationship of apical systolic murmur to underlying cardiac disease has not received due recognition. The consequences of failure to evaluate properly apical systolic murmur was brought to my attention during the late war, and it is to emphasize the result of underestimating this sign that additional material is presented. While serving with the navy, I saw in consultation large numbers of naval personnel in whom the sole objective symptom was a loud systolic murmur at the apex. In none of the cases was there enlargement of the heart; diastolic murmurs were not heard, electrocardiograms were not abnormal and signs of heart failure were not present. Yet the men and women concerned had been on the sick list for days, weeks or months. To the National Naval Medical Center at Bethesda, Md., which in the first year of the war, at least, was practically the last court of appeal for patients with troublesome conditions, came officers, marines, sailors, Waves and applicants for admission to the navy. Not only had they been examined by physicians in the armed forces but they often brought reports from civilian cardiac consultants. The latter frequently did not appreciate the fact that the stress and strain of war, physical and mental, has no counterpart in civilian life. That the patient's "cardiac function" was good was not proof that organic heart disease was absent or that the function would remain normal under war conditions. Unfortunately, Mackenzie [2] was responsible for the idea that an apical systolic murmur, no matter how loud, was not significant provided cardiac function was good and obvious signs of organic heart disease were not present.

In the South Pacific [3] there were many instances in which men complained of pain in the heart, fatigue and shortness of breath. Heart failure often developed in such instances. On examination it was found that they had definite signs of rheumatic valvular disease, and it was not surpising to discover that in many cases the histories revealed that in civilian life apical systolic murmurs had been a source of worry to their families and had created problems both for private physicians and for

1. Master, A. M.: (*a*) Evaluation of Systolic Murmurs, U. S. Nav. M. Bull. **42**:307 (Feb.) 1944; (*b*) Rheumatic Fever in the Navy, ibid. **41**:1019 (July) 1943; (*c*) The Problem of Rheumatic Fever in the Navy, Am. Heart J. **27**:634 (May) 1944; (*d*) Apical Systolic Murmurs in Incipient Rheumatic Heart Disease, Bull. New York Acad. Med. **22**:535 (Oct.) 1946.

2. Mackenzie, J.: Diseases of the Heart, New York, Oxford University Press, 1925, p. 361.

3. Footnote 1*a*, *b* and *c*.

physicians of insurance companies. At the time the men were examined for induction in the navy the recruiting medical officer had to face the problem of appraising the significance of the murmurs.

In the same area it became necessary, when ships had been sunk and health records lost, to reexamine officers and crew in order to obtain new records. During reexaminations instances of early but definite rheumatic heart disease were frequently encountered. It was found that when the men had been given physical examinations in civilian life and at the time of induction the question of significance of an apical systolic murmur had arisen. Furthermore, half of them gave a history of rheumatic fever.

In World War II the army also had to meet the problem of the apical systolic murmur. Levy, Stroud and White [4] considered it the most frequent, important and difficult problem met during cardiovascular examinations for military service and in the establishment of a diagnosis of organic valvular heart disease. They accepted "moderately loud" or "loud" apical systolic murmur as a cause for rejection of draftees. In civilian life evaluation of the apical systolic murmur is just as important and just as troublesome as it is in wartime. Heart failure may develop in patients with early rheumatic heart disease as a result of emotional stress, prolonged physical exertion, recurrence of rheumatic fever or infection with group A Streptococcus hemolyticus. The importance of the problem does not strike home in civilian life with the same dramatic force with which it did during wartme, but the situation arises as frequently and is as difficult to meet. Insurance statistics [5] show that loud apical systolic murmurs, even in the absence of enlargement of the heart, heart failure, diastolic murmurs or abnormal electrocardiograms, are a sign of organic heart disease. When the normally expected mortality rate for persons under 40 years of age was accepted as 100 per cent, the

4. Levy, R. L.; Stroud, W. D., and White, P. D.: Report of Reexamination of 4,994 Men Disqualified for General Military Service, J.A.M.A. **123**:937 (Dec. 11); 1029 (Dec. 18) 1943; Reexamination of 4,994 Men Rejected for General Military Service Because of the Diagnosis of Cardiovascular Defects, Am. Heart J. **27**:435 (April) 1944.

5. (*a*) Bonnett, E. C., and Low, E. A.: A Mortality Study of Systolic Heart Murmurs, Tr. A. Life Insur. M. Dir. America (1942) **29**:8, 1943. (*b*) Grosvenor, F. L.: Mitral Insufficiency—A Limited Experience, Including Etiology, abstracted, Proc. A. Life Insur. M. Dir. America **13**:199, 1926. (*c*) Hunter, A.: Heart Murmurs, Am. Heart J. **14**:10 (July) 1937. (*d*) Johann, A. E.: Apical Cardiac Murmurs, abstracted, Proc. A. Life Insur. M. Dir. America **14**:155, 1927. (*e*) McCrudden, F. H.: Heart Murmurs and Insurance, New England J. Med. **204**:598 (March 10) 1931. (*f*) Rogers, O. H., and Hunter, A.: Mortality Study of Impaired Lives: A. Inflammatory Rheumatism; B. Tuberculosis of Lungs and Blood Spitting, abstracted, Proc. A. Life Insur. M. Dir. America **9**:161, 1922; (*g*) Heart Murmurs—Their Influence on Longevity, abstracted, ibid. **6**:173, 1919. (*h*) Rockwell, T. H.: Experience on Risks with Mitral Regurgitation, Pract. Med. & Surg. **38**:347 (Feb.) 1933.

figure was 325 per cent for those with apical systolic murmurs, and when there was a history of rheumatic fever the rate rose to 453 per cent. The Metropolitan Life Insurance Company found somewhat similar figures in a study of mitral regurgitation.[6] Hunter [5c] learned that the mortality rate was 50 per cent higher among manual workers with apical systolic murmur than among "white collar workers." Furthermore, it is not infrequent to find unexpected evidence of a defect of the mitral valve and occasionally even of subacute bacterial endocarditis in patients in whom no symptoms had been noted previously except an apical systolic murmur which had been considered of little or no significance.[7] In fact, valvular disease is often overlooked during life and found only at death.

Since mitral valvular disease develops in 30 to 50 per cent of persons who have had rheumatic fever and since about 20 to 25 per cent of them fall victims to subacute bacterial endocarditis, it is essential that deformity of the mitral valve be recognized at an early stage. In many cases the earliest and only sign of disease of the mitral valve is a loud apical systolic murmur.

From the foregoing observations it should be evident that proper evaluation of a loud apical systolic murmur in the absence of enlargement of the heart, diastolic murmurs, abnormal electrocardiograms and heart failure is of paramount importance in medical practice both in war and in peace. I believe that this murmur should be accepted as evidence of organic valvular heart disease until cardiac abnormality can be disproved. I do not, of course, mean to imply that patients with apical systolic murmur necessarily should be considered invalids. The majority of them will undoubtedly lead perfectly normal lives, but they will not be able to undergo extremes of physical effort or to suffer long or severe emotional stress.

Use of the term "loud apical systolic murmur" here is based on the classification of Freeman and Levine,[8] who divided systolic murmurs into six grades: (1) extremely faint but of appreciable duration, (2) slight, (3) moderately loud, (4) loud, (5) extremely loud and (6) unusually loud. I have considered "loud" all apical systolic murmurs which fall within categories 3 to 6.

The following brief case reports illustrate the manner in which early heart disease may become manifest when the patient is exposed to ad-

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6. Medical Impairments and Mortality: Statistical Charts, Metropolitan Life Insurance Company, Scientific Exhibit of the American Medical Association, Milwaukee, Wis., 1933, chart 5, p. 9.

7. Zeman, F. D., and Siegel, S.: Acute Bacterial Endocarditis in the Aged, Am. Heart J. **29**:597 (May) 1945.

8. Freeman, A. R., and Levine, S. A.: The Clinical Significance of the Systolic Murmur: A Study of One Thousand Consecutive "Non-Cardiac" Cases, Ann. Int. Med. **6**:1371 (May) 1933.

verse conditions. The cases are taken from military and civilian experience.

Case 1.—J. S. A., a boy aged 17, had applied for induction in the navy. The recruiting officer heard an apical systolic murmur which he considered was organic in nature. The patient was rejected, but he was persistent and submitted the opinions of civilian cardiac consultants who pronounced the murmur functional. He was referred finally to the National Naval Medical Center at Bethesda, where I examined him early in 1943. Except for a prolonged systolic murmur at the apex, physical examination, fluoroscopic study and electrocardiograms revealed nothing abnormal. There was no history of rheumatic fever or of infection with Str. hemolyticus. However, the heart sound tracing gave evidence of a systolic murmur of prolonged duration from the first to the second sound (fig. 1). This was shown

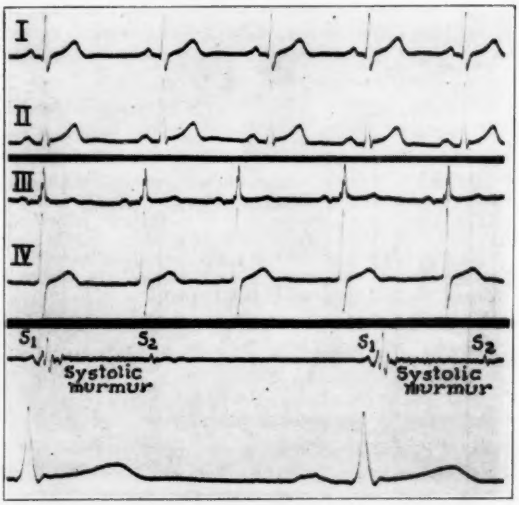

Fig. 1 (case 1).—Chronic cardiac valvular disease, with defect of the mitral valve. The heart was normal in roentgenograms and on fluoroscopy. The electrocardiogram, of which the four conventional leads are shown, is entirely normal, but the phonocardiogram reveals a prolonged murmur throughout the systole.

to the patient's physician as objective proof of an organic lesion, and the young man was advised to abandon the idea of entering the armed forces. The matter was considered closed.

Sometime later, while making rounds on a ward for cardiac patients in a Naval Hospital in the Pacific, I found J. S. A. in bed with heart failure. He had been admitted with advanced pulmonary congestion. On questioning him, I found that he had continued his attempts to enter the navy and had finally been accepted for the Marine Corps. Although he had at first performed his duties without difficulty, his cardiac condition flared up during the invasion of Guam and pulmonary edema ensued.

It is interesting to note that even during and after development of heart failure the patient's heart was not enlarged. It is generally believed that enlargement of the heart is concomitant with heart failure, but in

early cases enlargement may not be apparent. Perhaps the enlargement is relative and not absolute. This case illustrates the fact that a long (holosystolic) murmur should be accepted as evidence of organic valvular heart disease unless this interpretation can be shown to be untenable.

CASE 2.—W. J. F., a married woman aged 27, was first seen during May 1941. Sudden hemoptysis had developed, followed a few days later by pulmonary edema. Physical examination revealed mitral stenosis; there was a presystolic murmur at the apex, a loud first mitral sound and a loud second pulmonic sound. The past history was noncontributory except that during the last six years she had had an apical systolic murmur which was discovered accidentally. This murmur was considered to be of organic nature by only one of the many physicians whom she had consulted.

The patient had given birth to two children, each of whom survived only a few months. The second child had recently died of Niemann-Pick disease. The mother became prostrated, and the emotional factor had undoubtedly precipitated the acute episode of hemoptysis and pulmonary edema.

A teleoroentgenogram showed that the heart was somewhat pendulous and that there was straightening of its left border, that is, the region of the pulmonary artery was prominent. Fluoroscopic examination revealed that the left auricle was enlarged although the left main bronchus was not elevated. Electrocardiographically there was no definite evidence of disease of the valve or of the muscle. The P wave in lead III was inverted.

CASE 3.—W. H., aged 22, was seen in consultation at the United States Naval Hospital, St. Albans, Long Island, on April 4, 1945. A history of chorea at the age of 7 years and of repeated nosebleeds between the ages of 5 and 17 years was given. A systolic thrill was palpable at the apex, and a harsh prolonged systolic murmur was heard in the mitral and apical areas. The first sound was loud, and the pulmonic second was accentuated. The blood pressure was 126 systolic and 86 diastolic. After exercise, a presystolic murmur was heard.

A roentgenogram showed that the heart was not enlarged but that there was prominence in the region of the pulmonary artery. In the left oblique position the left auricle was enlarged; the left main bronchus was not elevated. The electrocardiogram showed no abnormality. The phonocardiogram revealed a prolonged systolic murmur over the mitral area. At the pulmonic and aortic areas the murmurs were not so prolonged.

It is clear that the harsh prolonged systolic murmur was due to defect of the mitral valve.

CASE 4.—R. J. M., a marine aged 25, was seen on June 5, 1945, at the United States Naval Hospital, St. Albans, Long Island. The patient had rheumatic fever at the age of 11 years. When he was at the age of 12, application for insurance was refused. He enlisted in the army in 1940 but was discharged in 1942 with a diagnosis of valvular heart disease. In 1943 he was inducted into the Marine Corps because the recruiting officer could not find evidence of organic heart disease. In May 1945 he complained of dyspnea on exertion and occasional sharp precordial pain.

On examination at St. Albans, a loud, blowing apical systolic murmur was heard, which was "sea-gull" in character; the first sound was snappy and the second pulmonic sound accentuated. The blood pressure was 126 systolic and 68 diastolic. The teleoroentgenogram showed that the left border of the heart was

straightened and the right border was increased in convexity (fig. 2*A*). In the left oblique position the left auricle was enlarged and filled in the space below the left main bronchus (fig. 2*B*). The electrocardiogram revealed a tendency toward right axis deviation. Even more significantly, the phonocardiogram disclosed a systolic murmur throughout the systole (fig. 4*C*).

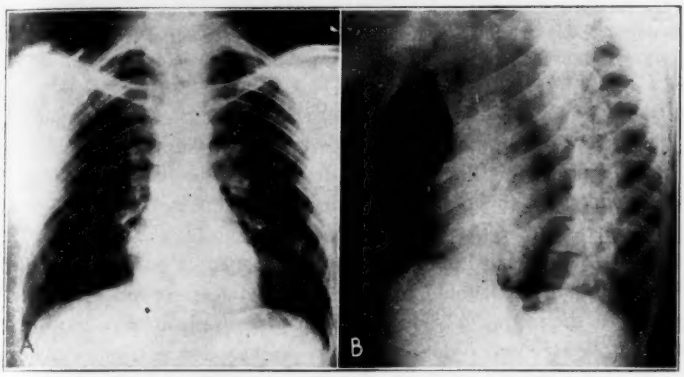

Fig. 2 (case 4).—*A*, chronic rheumatic cardiac valvular disease, with involvement of the mitral valve. The heart is not enlarged, but the right border is convex, and the left border is straight in the region of the pulmonary arc and the left auricular appendage. *B*, in the left oblique position may be seen the enlarging left auricle filling in the space beneath the left main bronchus. The latter, however, is not elevated.

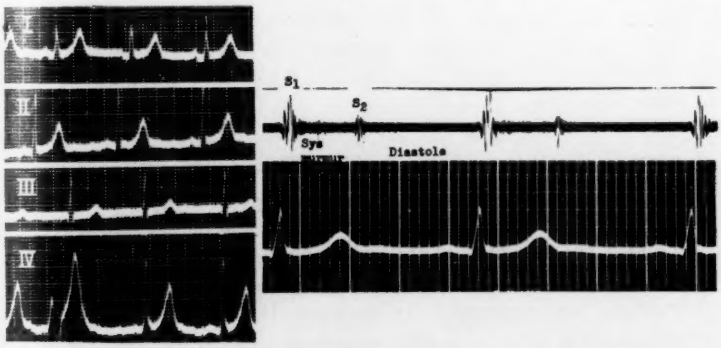

Fig. 3 (case 5).—Chronic rheumatic cardiac valvular disease, with involvement of the mitral valve. The electrocardiogram is normal. The phonocardiogram reveals a high-pitched systolic murmur throughout the systole and a short early diastolic murmur.

The history of rheumatic fever, the "sea-gull" character of the murmur and its prolonged nature on the phonocardiogram, the roentgenographic and fluoroscopic evidence of an enlarged left auricle, and the right axis deviation in the electrocardiogram were proof of the organic nature of the loud apical systolic murmur.

Case 5.—D. W., aged 21, was admitted in April 1945 to the United States Naval Hospital, St. Albans, Long Island, with rheumatic fever. When he was seen in consultation on May 17, 1945, a prolonged systolic murmur was heard at the apical region. After exercise, this murmur took on a "sea-gull" character. The blood pressure was 140 systolic and 78 diastolic.

Roentgenologic examination showed that the heart was not enlarged; it was globular in shape. In the left oblique position the left auricle was enlarged but the left main bronchus was not elevated. The electrocardiogram was normal (fig. 3), but the phonocardiogram revealed a high-pitched systolic murmur and a short diastolic murmur (fig. 3).

The presence of rheumatic fever, a "sea-gull" quality of the murmur, a globular-shaped heart, left auricular enlargement, and phonocardiographic evidence proved the organic nature of the prolonged apical systolic murmur at the apex.

DIAGNOSIS

To determine whether a patient who exhibits a systolic murmur at the apex has organic heart disease, resort must be had to the information provided by the patient's history and by physical and laboratory examination.

History.—A record of rheumatic fever for a patient with a loud apical systolic murmur should be accepted as almost certain evidence that a defect of the mitral valve exists. Likewise, the history of an infection by group A. Str. hemolyticus must now be regarded as of similar significance. Many recent articles [9] afford proof of the relationship of this type of infection to rheumatic fever and rheumatic heart disease.

Physical Examination.—The value of repeated examination of patients who have a questionable systolic murmur cannot be emphasized too strongly. Frequently the presence of a murmur can be established only after examination in different positions and after exercise, because in cases of early valvular heart disease the murmurs are transient. When I have difficulty in coming to a decision, I routinely examine the patient at least three times.

In the early stages of valvular heart disease the heart is not enlarged, an apex thrill is not usually palpable and diastolic murmur is not routinely audible. The first sound at the apex is loud, as is the second pulmonic sound. The murmur at the apex is loud and prolonged; it begins and is concurrent with the first sound. The presence of "musical" murmur, "sea-gull" murmur, "harsh" murmur or "constant" murmur strengthens the diagnosis. As early as 1832, Hope [10] described the evanescent character of mitral murmurs. The left lateral recumbent position and the sitting position, with the patient leaning forward and to the left, are the most advantageous for examination. Repeated exami-

9. Watson, R. F.; Rothbard, S., and Swift, H. F.: The Relationship of Post-scarlatinal Arthritis and Carditis to Rheumatic Fever, J.A.M.A. **128**:1145 (Aug. 18) 1945. Suarez, R. M.: The Incidence of Heart Disease in Puerto Rico: Statistical Analysis of 1,081 Cases, Am. Heart J. **29**:339 (March) 1935. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945. Connor, C. A. R.: Experiences with Rheumatic Fever in the Army Air Forces, Am. J. Pub. Health **36**:236 (March) 1946.

10. Hope, J.: A Treatise on the Diseases of the Heart, London, W. Kidd, 1832.

nations may not only elicit a loud apical systolic murmur which persists for some time but may also disclose the presence of a diastolic murmur, thereby confirming the diagnosis of disease of the mitral valve. A systolic murmur at the apex produced by exercise is not necessarily evidence of organic heart disease. The murmur indicative of heart disease is loud and prolonged and persists for a longer period than is to be expected from the effect of exercise alone. Effort, particularly if strenous, produces murmurs in a healthy person, but these disappear almost immediately after cessation of exertion and certainly as the heart rate slows. Moreover, such murmurs are not loud. Freeman and Levine [8] found that in healthy persons murmurs of grades 1 and 2 were common after exercise but that grade 3 murmurs did not appear. Friedlander and Brown [11] substantiated this observation.

Inhalation of amyl nitrite has been advocated [12] as a method of bringing out loud, harsh, prolonged, persisting systolic murmurs and of disclosing the presence of a diastolic murmur, particularly a presystolic one. Friedlander and Brown [11] stated that they never heard a "loud" murmur after administration of amyl nitrite to normal persons. An objection to the use of amyl nitrite arises from that fact that it causes distressing headache at times. It should be used only if the patient is unable to exercise.

Teleoroentgenograms and Fluoroscopy.—In early disease of the mitral valve, neither teleoroentgenographic nor fluoroscopic study reveals cardiac enlargement, elevation of the left main bronchus, the appearance of a left auricular arc far over the right side of the heart or indentation of the barium-filled esophagus. These abnormalities are revealed only in cases of well established disease of the mitral valve. There are, however, two important diagnostic signs to be observed in beginning involvement of the mitral valve. Fluoroscopic examination in the left oblique position shows the space beneath the left main bronchus filled by the expanding auricle.[13] "Straightening" of the left border of the heart caused by the prominence in the region of the pulmonary artery may also be seen.[13a] This bulge, according to Grishman, Sussman and Steinberg,[14] is produced as the enlarging left auricle pushes the pulmonary artery up and to the

11. Friedlander, R. D., and Brown, M. G.: The Systolic Murmur: Further Observations on Its Clinical Significance, Ann. Int. Med. **8**:893 (Feb.) 1935.

12. Fahr, G.: The Significance of the Systolic Murmur, Nebraska M. J. **15**:458 (Dec.) 1930. Friedlander and Brown.[11]

13. Ungerleider, H. E., and Gubner, R.: Roentgenology of the Heart and Great Vessels, in Stroud, W. D.: Diagnosis and Treatment of Cardiovascular Disease, ed. 3, Philadelphia, F. A. Davis Company, 1945, p. 789. Master.[13a]

14. Grishman, A.; Sussman, M. L., and Steinberg, M. F.: Angiocardiographic Analysis of the Cardiac Configuration in Rheumatic Mitral Disease, Am. J. Roentgenol. **51**:33 (Jan.) 1944.

left. Fineberg and Steuer [15] and also Wolfson [16] stress the help to be obtained from the roentgenogram.

Phonocardiogram.—The phonocardiogram is a useful adjunct in establishing the presence of disease of the mitral valve. [17] When the length of a murmur cannot be accurately determined, this sound-recording apparatus may reveal that the systolic murmur is a long one, occurring throughout the entire systole, that is, "holosystolic." Futhermore, the stethograph may demonstrate the presence of an otherwise inaudible diastolic murmur.

It is not necessary that every practitioner should own or routinely use a heart sound machine, but resort to a recording apparatus may be helpful in the type of case under discussion.

Bass and his colleagues,[18] from a study of systolic murmurs in children, reported that the murmurs heard in cases of organic lesions disclosed low frequency as well as high frequency components whereas functional murmurs exhibited only high frequency vibrations.

Electrocardiogram.—On occasion the electrocardiogram may be of value in diagnosing beginning defect of the mitral valve. Right axis deviation of the QRS complex, a P wave of more than 2.5 mm. in height or at least 0.10 second in time or a distinctly notched wave are signs of deformity of the mitral valve.[19] Enlargement of the right side of the heart produces right axis deviation of the QRS waves. The abnormalities of the P wave are due to enlargement of the left auricle or to a change in its position or shape or to a combination of these factors.

DIFFERENTIAL DIAGNOSIS

Neurocirculatory asthenia, or effort syndrome or "small heart syndrome," [20] must be considered in the differential diagnosis of disease of the mitral valve. In neurocirculatory asthenia a systolic thrill may be palpated and a loud apical systolic murmur may be heard on auscultation concomitantly with a loud first sound at the apex and a loud second

15. Fineberg, M. H., and Steuer, L. G.: Apical Systolic Murmurs in Children: Follow-Up Observations in One Hundred Cases, Am. Heart J. **7**:553 (June) 1932.

16. Wolfson, I. N.: Clinical and Laboratory Studies of Ninety-One Workers with Apical Systolic Murmurs, New England J. Med. **233**:757 (Dec. 20) 1945.

17. Bartlett, W. M.: Combined Electrocardiography, Stethography and Cardioscopy in the Selection of Pilots, J. Aviation Med. **12**:2 (March) 1941.

18. Bass, M.; Mond, H.; Messeloff, C., and Oppenheimer, E.: The Systolic Murmurs in Children, J.A.M.A. **101**:17 (July 1) 1933.

19. (*a*) Berliner, K., and Master, A. M.: Mitral Stenosis: A Correlation of Electrocardiographic and Pathologic Observations, Arch. Int. Med. **61**:39 (Jan.) 1938. (*b*) Master, A. M.: The Electrocardiogram and X-ray Configuration of the Heart, ed. 2, Philadelphia, Lea & Febiger, 1942, p. 148. (*c*) White, B. V.; Parker, R. C., Jr., and Master, A. M.: Disease of the Mitral Valve: Its Effect on the Pattern of the Electrocardiogram, Arch. Int. Med. **74**:94 (Aug.) 1944.

20. Master, A. M.: Neurocirculatory Asthenia Due to Small Heart, M. Clin. North America **28**:577 (May) 1944.

pulmonic sound. To add to the difficulty of differentiation, the roentgenogram demonstrates a straight left border of the heart and the electrocardiogram may disclose the abnormalities previously described for disease of the mitral valve.[21] The differentiation can usually be made on the basis of other, well recognized symptoms of neurocirculatory asthenia. The patient is nervous, reveals a tremor and complains of dizziness and giddiness and often of severe precordial pain unrelated to effort. Symp-

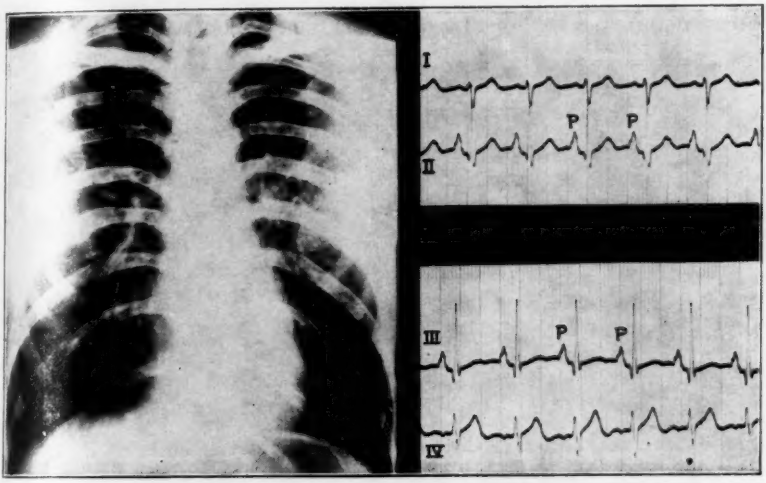

Fig. 4 (case 6).—Effort syndrome (small heart syndrome, or neurocirculatory asthenia). The diaphragm is in a low position, with a long, pendulous, narrow heart. The electrocardiogram reveals right axis deviation of the QRS waves, low amplitude in lead I and relatively large amplitude in leads II and III. The P (auricular) waves are large.

toms of an anxiety neurosis are also present. Moreover, neurocirculatory asthenia almost always appears in long thin persons having low diaphragms and long, narrow or small hearts. The following history is characteristic of this type of patient.

Case 6.—H. T. H., aged 31, was seen at the National Naval Medical Center on Jan. 30, 1943. His weight was 120 pounds (54 Kg.) and his height 5 feet 10 inches (178 cm.). The past history was noncontributory. He was referred to the center because of a questionable systolic murmur. An electrocardiogram had disclosed right axis deviation, with large P waves. On examination a blowing systolic murmur was heard at the apex. A teleoroentgenogram showed that the diaphragm was low in position and that the heart was narrow and pendulous (fig. 4).

An electrocardiogram revealed right axis deviation of the QRS complex and low amplitude in lead I, with relatively high amplitudes in leads II and III. The P waves were tall (fig. 4). The diagnosis of neurocirculatory asthenia was made because the man was tall and thin and because the roentgenogram revealed a low diaphragm and a narrow pendulous small heart.

21. Master (footnotes 1*a*, 19*b* and 20).

Deformity of the Chest.—A funnel-shaped chest or merely a thin, flat chest may give rise to signs of mitral valve disease.[22] Not only does a person of this bodily formation exhibit harsh apical systolic murmur but the heart often appears to be enlarged and the left border straightened. Careful examination permits differentiation from disease of the mitral valve. Viewed in an oblique or a lateral position by means of the fluoroscope or in roentgenograms the sunken sternum and the narrow space between the breast bone and the vertebral column become apparent. In these deformities the heart is pushed and rotated into the left side of the

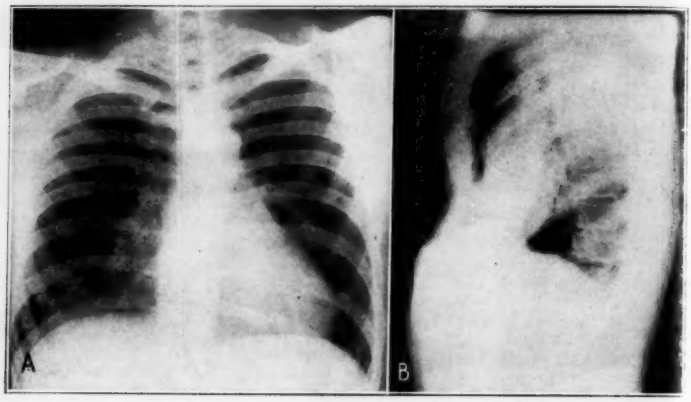

Fig. 5 (case 7).—*A*, funnel-shaped chest. In the teleoroentgenogram the heart is seen to be entirely on the left side. The right border is hidden behind the vertebral column, and the left border is straight. *B*, the left lateral view shows the depressed sternum producing the small anterioposterior diameter of the heart.

chest. The spinal column appears to be the right border of the heart, and since the left border is displaced to the left the heart appears to be large but really is not. The next case is an example of this type of deformity.

Case 7.—W. H. M., a marine aged 19, weighed 195 pounds (88.5 Kg.), and was 6 feet (183 con.) tall. Pain in the chest and shortness of breath developed during the invasion of Saipan. On examination a systolic murmur was heard at the apex, but a pronounced depression was found at the lower end of the sternum. The electrocardiogram revealed abnormal P waves.

The teleoroentgenogram disclosed that the heart was displaced to the left (fig. 5*A*). A lateral view and a fluoroscopic examination showed marked diminution in the anterior-posterior diameter of the heart (fig. 5*B*).

The vital capacity was 3,600 cc., a figure that is low for a person of this size.

The definite depression of the lower part of the chest and the disclosure by lateral view roentgenograms and also by fluoroscopy of an extremely narrow anterior-posterior diameter established the diagnosis of funnel-shaped chest.

22. Master,[19b] p. 349.

Kyphoscoliosis.—Life deformity of the chest, kyphoscoliosis may enter into the problem of differentiation.[22] When the scoliosis is toward the right in the dorsal region, the heart is displaced to the left, the left border appears straightened, that is, "mitralized," and the heart itself seems to be enlarged. The enlargement is, however, only apparent; actually the right edge of the dorsal vertebrae is mistaken for the right border of the heart. As with a funnel-shaped or a flat chest, a loud apical systolic murmur is heard and much the same electrocardiographic changes are observed.

A Split First Sound.—A split first sound occasionally simulates systolic murmur, and at times it may even resemble the presystolic murmur which arises from deformity of the mitral valve. Careful timing of the sounds and especially a phonocardiographic tracing permit a correct diagnosis[1a] to be made. Both sounds occur early in systole, and they have the relatively large amplitude of heart sounds rather than the smaller amplitude of murmurs. They are practically equal in height and do not appear in diastole.

Hypertension.—In hypertension a prolonged apical systolic murmur is not infrequently heard. The patients have high blood pressure of long standing, enlargement of the heart and elongated tortuous dense aorta.[23] Usually they are middle-aged or old and present evidence of generalized arteriosclerosis.

Hyperthyroidism.—In hyperthyroidism an apical systolic murmur may be heard, but the characteristic signs and symptoms of this disease distinguish it from rheumatic heart disease.[24] An increased heart rate and an elevated basal metabolic rate point to exophthalmic goiter. Occasionally the two diseases are found in the same person, and many investigators are of the opinion that the milieu of hyperthyroidism provides fertile soil for rheumatic heart disease.[25]

Anemia.—Anemia, primary or secondary (not uncommonly the latter), gives rise to loud systolic murmurs heard best at the apex on auscultation. The blood count is, of course, the feature that distinguishes anemia from disease of the mitral valve. Theoretically, secondary anemia occurring in conjunction with rheumatic fever or rheumatic heart disease might create difficulty in differential diagnosis; actually, the valvular defect is obvious.

Respiratory Murmurs.—The question of respiratory murmurs frequently enters into the differential diagnosis, though usually not to an

23. Master,[10b] p. 114.

24. Master,[10b] p. 276.

25. Maher, C. C.; Sanders, A.; Plice, S. G., and Wosika, P. H.: A Syndrome of Exophthalmic Goiter, Acute Rheumatic Carditis and Heart Block, Am. Heart J. **17**:742 (June) 1939.

important degree. Thayer [26] in 1925 pointed out that respiratory murmurs are accentuated during inspiration and usually disappear at some stage of respiration, generally when a full breath is maintained. Sodeman [27] noted that if the patient stops breathing at the end of a full inspiration or expiration or even at any point in the cycle the murmur disappears. As a matter of fact, holding the breath at any phase in breathing generally causes a respiratory murmur to vanish.

COMMENT

A loud systolic murmur at the apex should be considered organic in nature until is can be proved to be of other origin. The patients should be treated accordingly even when evidence of past rheumatic fever, enlargement of the heart, diastolic murmur, abnormal electrocardiogram, or heart failure is lacking. Such patients should receive antibiotics during various manipulations and diseases which injure the mucous membrane and facilitate the entrance of bacteria into the blood stream which may lead to bacterial endocarditis. The diseases include infections in the ear, nose and throat and genitourinary system and the procedures include operations on the ear, nose and throat and genitourinary system.

A history of rheumatic fever or evidence of infection by group A Str. hemolyticus affords confirmatory evidence of the organic origin of a loud apical systolic murmur, but in 20 to 25 per cent of patients, or perhaps in a larger percentage, such evidence is not found. Some years ago Scott [28] and Hedley [29] pointed this out. Recently Flaxman [30] reported that among men rejected for the army in World War II because of systolic murmur of organic valvular origin only 48 per cent gave a history of previous rheumatic fever. Levy, Stroud and White [4] reported even a lower figure, i.e., 28.8 per cent.

That apical systolic murmurs be properly interpreted is of first importance because correct diagnosis may depend on correct evaluation of these murmurs. It should be kept in mind constantly that the sound of these murmurs varies; they may be loud in one examination and not audible in the next, and they vary with alteration in the position of the

26. Thayer, W. S.: Reflections on the Interpretation of Systolic Cardiac Murmurs, Am. J. M. Sc. **169**:313 (March) 1925.

27. Sodeman, W. A.: The Systolic Murmur, Am. J. M. Sc. **208**:106 (July) 1944.

28. Scott, R. W.: The Significance of the Systolic Murmur, abstracted, Proc. Life Insur. M. Dir. America **21**:114, 1934.

29. Hedley, O. F.: Studies of Heart Disease Mortality: An Analysis of the Accuracy of Deaths Recorded as Being Due to Heart Disease in Washington, D. C., During 1932, with a Discussion of the Defects of the Present Method of Tabulating Deaths, and Suggestions for a New System Based upon Etiological Factors, Bulletin 231, United States Treasury Department, Public Health Service, 1936.

30. Flaxman, N.: Initial Cardiac Examination of Twenty-Three Thousand Inductees and Volunteers, Am. J. M. Sc. **209**:657 (May) 1945.

patient. They may disappear for weeks, months or years and then reappear. They may vanish permanently. Coombs [31] reported that in 31 per cent of cases the symptoms of rheumatic heart disease regressed. Bland, Jones and White [32] in a follow-up study of 1,000 patients with valvular disease observed that physical signs became less apparent in a considerable number and that in 83 cases all physical signs vanished permanently. Wilson [33] made similar discoveries. I have observed a man 31 years old who had rheumatic fever and large pericardial effusion. Later there was definite evidence of mitral and aortic disease, with enlargement of the heart. Nevertheless the patient was completely free of all signs at the end of three years. Many cardiologists have encountered similar instances. Swift [34] expressed the opinion that rheumatic valvulitis may clear up entirely in much the same way that the swollen ankle heals in rheumatic fever. Wilson [33] stated the belief that minimal scarring of the valve remains. Her opinion is probably correct, because postmortem examination frequently discloses evidence of old rheumatic heart disease that was not suspected during life or at least during the last years of life. As early as 1832 Hope [10] noted absence of any murmur even in "tight" mitral stenosis; Flaxman [35] observed this recently. In fact, White [36] stated that in half of the cases of mitral stenosis the disease would remain undiagnosed if the diagnosis were based solely on the presence of presystolic murmur.

In the evaluation of apical systolic murmurs, the loudness or the intensity of the murmur is of more significance than its transmission. As Levine and Likoff [37] showed, the louder the murmur the greater the transmission. Scott,[28] Levine,[38] Sodeman [27] and Shapiro [39] expressed the belief that the importance of a murmur increases with its loudness.

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31. Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood & Company, 1924.

32. Bland, E. F.; Jones, T. D., and White, P. D.: Disappearance of the Physical Signs of Rheumatic Heart Disease, J.A.M.A. **107**:569 (Aug. 22) 1936.

33. Wilson, May G.: Rheumatic Fever: Studies of the Epidemiology, Manifestations, Diagnosis, and Treatment of the Disease During the First Three Decades, New York, The Commonwealth Fund, 1940, p. 393.

34. Swift, H.: Personal communication to the author.

35. Flaxman, N.: Historical Aspects of Mitral Stenosis, M. Rev. of Rev. **42**:461 (Nov.) 1936.

36. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944, p. 81.

37. Levine, S. A., and Likoff, W. B.: Some Notes on the Transmission of Heart Murmurs, Ann. Int. Med. **21**:298 (Aug.) 1944.

38. Levine, S. A.: The Systolic Murmur: Its Clinical Significance, J.A.M.A. **101**:436 (Aug. 5) 1933.

39. Shapiro, M. J.: Follow-Up Study of Systolic Murmurs, Am. Heart J. **17**:416 (April) 1939.

White,[40] in a report on the clinical significance of apical heart murmurs in 1,000 patients, stated that loud murmurs were almost always an indication of an abnormal heart. It is of interest that in the aged, too, loud apical systolic murmurs have been found to signify organic heart disease.[7]

SUMMARY

Experience during the recent war brought into prominence the consequences of failure to recognize apical systolic murmur as an indication of organic disease of the mitral valve. Army and Navy personnel with such murmurs had to be reexamined frequently, lost valuable time in hospitals, were a burden to the government and a source of additional expense. Finally, in certain instances, heart failure developed under the mental and physical exigencies of war.

Similarly, in civilian life cardiovascular complaints and even heart failure may be precipitated by emotional stress, physical exertion, recurrence of rheumatic fever or infection with group A Str. hemolyticus.

For adequate protection of patients, loud systolic murmurs at the apex unaccompanied with a systolic thrill, an enlarged heart, diastolic murmur, an abnormal electrocardiogram and evidence of heart failure should be most carefully appraised. According to insurance statistics, the mortality rate for persons with this murmur is increased. Hard physical work may shorten the span of life.

Defect of the mitral valve or even subacute bacterial endocarditis may suddenly become apparent in persons in whom the only sign of organic valvular disease has been the presence for years of apical systolic murmur.

Seven cases are cited to illustrate the diagnostic criteria required to appraise the significance of apical systolic murmur.

A history of rheumatic fever or of infection with group A Str. hemolyticus given by a patient with a loud apical systolic murmur should be accepted as almost certain evidence of defect of the mitral valve.

The diagnostic signs to be sought in physical examination are a loud first apical and a loud second pulmonic sound. A prolonged murmur is significant. A "musical," "sea-gull," "harsh" or "constant" murmur tends to confirm the presence of organic heart disease.

Patients should be examined repeatedly, in different positions and after exercise, since the murmurs of early valvular heart disease are transient. Such careful investigation may disclose not only a loud systolic murmur but also a diastolic murmur. It is only in cases of advanced heart disease that one finds a distinct systolic thrill, enlargement of the heart, diastolic murmurs, abnormal electrocardiograms and signs of heart failure.

Murmurs following exertion are significant only when they are loud and prolonged and persist after the heart rate has slowed. Inhalation of amyl nitrite may serve to elicit heart sounds if a patient is unable to exercise.

40. White, P. D.: The Clinical Significance of Apical Heart Murmurs, Am. J. M. Sc. **174**:732 (Dec.) 1927.

Two signs of beginning mitral valve deformity are to be seen in roentgenograms and on fluoroscopic examination. In the left oblique position the space beneath the left main bronchus is filled by the enlarging left auricle. In the posterior-anterior view the left border of the heart may be "straight," a result of prominence in the region of the pulmonary artery. Only in long established disease of the mitral valve does one find cardiac enlargement, elevation of the left main bronchus produced by the large left auricle, a left auricular arc far over on the right side of the heart or indentation of the barium-filled esophagus.

The phonocardiogram may prove helpful in establishing the duration of a systolic murmur and may demonstrate an otherwise inaudible diastolic murmur. The electrocardiogram is most helpful in the diagnosis of advanced involvement of the mitral valve, but occasionally when there is early impairment it reveals abnormal P (auricular) waves and right axis deviation.

Neurocirculatory asthenia frequently offers a problem in differential diagnosis. However, patients with this disease commonly present symptoms of anxiety neurosis. In addition, they are usually of the asthenic type, with a low diaphragm and a long, narrow, small heart.

Funnel and flat-shaped chests and kyphoscoliosis involving the right dorsal area often cause symptoms which simulate those of rheumatic involvement of the mitral valve. Mere inpection of the chest, roentgenograms and fluoroscopic examination demonstrate the deformity. Occasionally a split first sound is mistaken for a systolic murmur. Its occurrence in early systole distinguishes it from the latter.

Hypertension, hyperthyroidism and anemia can produce loud apical systolic murmurs. The diagnostic characteristics of these illnesses demarcate them from disease of the mitral valve.

The respiratory murmur is characterized by its relation to breathing and its disappearance when the breath is held.

There may be organic disease of the mitral valve without a history of rheumatic fever. The physical signs of rheumatic heart disease may regress. These developments make it harder to evaluate the significance of apical systolic murmurs, but a knowledge of all the difficulties, including these and others previously described, is a necessary step in their solution.

Establishment of the organic nature of a murmur does not afford a criterion of the heart's function. Patients may be able to live a normal life to a ripe old age. Unsuspected rheumatic disease of the mitral valve not infrequently is first discovered in old age or even at autopsy.

The loudness of a systolic murmur is of more diagnostic value than its transmission. The latter depends on the intensity of the murmur. A loud apical systolic murmur should be accepted as evidence of organic mitral valve disease until this is disproved. A "loud" murmur is not heard in normal hearts of either young or old.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1946 to July 1947

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INTRODUCTION

As in preceding years, this review does not include the liver, gallbladder, biliary tract or pancreas. Nevertheless the size of the task is indicated by the fact that the present review is based on an analysis of more than six hundred articles. Every effort has been made to incorporate all worth while contributions, but the reviewers recognize the possibility that some valuable papers may have been unintentionally overlooked.

The gastroenterologic literature for the past year consists chiefly of interesting and useful clinical observations, statistical analyses and case studies. The variety and the volume of the recorded clinical material are truly impressive. Nearly one fifth of the review is composed of articles on peptic ulcer. Many of the reports deal with advances in surgical technic. There has been a relative scarcity of papers devoted primarily to research, approximately 20 per cent; indeed, only a small percentage of these deal with basic problems in gastroenterology.

BOOKS

Numerous texts on various phases of gastroenterology [1] have been published during this period. Because of the length of the review, it has seemed advisable to comment briefly on only a few of these. Many of the foreign books have not been available to the reviewers. Turner [1a] discusses informally his extensive experience with injuries and diseases of the esophagus. The second edition of "Human Gastric Function" by Wolf and Wolff [1d] maintains the high quality of the first edition of this competent and significant study of gastric physiology. Schindler [1e] has comprehensively analyzed his twenty-five years' experience with gastritis

1. (*a*) Turner, G. G.: Injuries and Diseases of the Esophagus, London, Cassel & Co., 1947. (*b*) Collett, F. J.: Les troubles de l'innervation pharyngolaryngée et esophagienne, Paris, Masson & Cie, 1946. (*c*) Buchs, S.: Die Biologie des Magenkathepsins: Experimentelle Untersuchungen zur Physiologie und Fermentchemie der Eiweissverdauung in Magen, Basel, S. Karger, 1947. (*d*) Wolf, S., and Wolff, H. G.: Human Gastric Function; An Experimental Study of a Man and His Stomach, New York, Oxford University Press, 1947. (*e*)

in a book which should interest all students of the subject. Ulcer of the stomach, duodenum and jejunum is clearly portrayed by Brown.[1f] "The Radiologic Examination of the Small Intestine" by Golden,[1j] the second edition of Wangensteen's "Intestinal Obstruction" [11] and the ninth edition of Cope's "The Early Diagnosis of the Acute Abdomen" [1o] are valuable books by outstanding authorities. Brunschwig [1s] presents a detailed and interesting analysis of the results of radical surgical intervention in 100 unselected patients with advanced abdominal cancer. Other American texts include Fradkin's [1p] "Diagnosis and Treatment of Diarrheal Diseases," Spiesman's [1q] "Essentials of Clinical Proctology" and Pelner's [1k] "Gastroenterology in General Practice."

ESOPHAGUS

General.—Howard [2] discusses the value of esophagoscopy and recommends its more frequent application by gastroenterologists.

Esophagogastroscope.—A new type of esophagoscope has been developed by Boros.[3] The outstanding feature of the instrument is the softness and extreme mobility of its tip, facilitating passage beyond the pharynx into the esophagus and even into the stomach without the attendant dangers of the rigid, unyielding instrument.

Congenital Atresia.—The roentgen features of congenital atresia of the esophagus in 45 consecutive patients with this anomaly are described,

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Schindler, R.: Gastritis, New York, Grune & Stratton, Inc., 1947. (*f*) Brown, R. C.: Ulcer of the Stomach, Duodenum and Jejunum, New York, Oxford University Press, 1946. (*g*) Nasio, J.: Tratamiento medico de la ulcera gastroduodenal experimental, Buenos Aires, La prensa medica argentina, 1946. (*h*) Laureys, S.: Pathogenie de l'ulcere rond, cancer, syphilis et autres maladies, Antwerp, the Author, 1946. (*i*) Maingot, R.; Technique of Gastric Operation, London, Oxford University Press, 1946. (*j*) Golden, R.: Radiologic Examination of the Small Intestine, Philadelphia, J. B. Lippincott Company, 1946. (*k*) Pelner, L., and Held, L. A.: Gastroenterology in General Practice, Springfield, Ill., Charles C Thomas, Publisher, 1947. (*l*) Wangensteen, O. H.: Intestinal Obstructions, ed. 2, ibid., 1947. (*m*) McNeill, R. J.: The Appendix, London, H. K. Lewis & Co., Ltd., 1946. (*n*) Short, A. R.: The Causation of Appendicitis, Bristol, John Wright & Sons, Ltd., 1946. (*o*) Cope, Z.: The Early Diagnosis of the Acute Abdomen, ed. 9, New York, Oxford University Press, 1946. (*p*) Fradkin, W. Z.: The Diagnosis and Treatment of Diarrheal Diseases, New York, Grune & Stratton, Inc., 1947. (*q*) Spiesman, M. G.: Essentials of Clinical Proctology, ibid., 1947. (*r*) d'Allaines, F.; LeRoy, A., and Dubost, C.: Traitement chirurgical du cancer du rectum, Paris, Ernest Flammarion, 1946. (*s*) Brunschwig, A.: Radical Surgery in Advanced Abdominal Cancer, Chicago, University of Chicago Press, 1947. (*t*) Cameron, T. W. M.: The Parasites of Man in Temperate Climates, Toronto, Canada, University of Toronto Press, 1947.

2. Howard, J. T.: Adventures in the Esophagus, South. M. J. **40**:197-206, 1947.

3. Boros, E.: Esophagoscopy by Means of a Flexible Instrument: A New Esophago-Gastroscope, Gastroenterology **8**:724-728, 1947.

42 of whom also had tracheoesophageal fistula.[4] Congenital partial atresia of the esophagus associated with congenital diverticulum of the esophagus [5] and a case of congenital atresia of the esophagus in which a segment of the esophagus was absent, both sections ending blindly in the thorax, also are recorded.[6] Ladd and Swenson [7] describe the surgical technic for the treatment of esophageal atresia and tracheoesophageal fistula, utilizing a retropleural approach through the right thoracic region of the back; the operation was successful in 30 of 76 babies. A patient with complete atresia of the esophagus and tracheoesophageal fistula was operated on successfully by means of an end to end anastomosis.[8]

Spontaneous Rupture.—Three consecutive cases of fatal spontaneous rupture of the esophagus were observed by Eliason and Welty [9] in one year; in the patient described by Frink [10] recovery occurred without operation.

Perforation.—Perforation of the esophagus by a foreign body, producing a putrid pulmonary abscess,[11] and penetration of the esophagus by a small bone eroding into the aorta [12] are described. Retropharyngeal perforation of the esophagus occurred during gastroscopy after considerable manipulation of the instrument.[13]

Foreign Bodies.—A frequently observed roentgen sign of foreign bodies in the esophagus, according to Johnstone,[14] is the presence, on swallowing, of a bolus of air in the segment containing the foreign body. The only other condition which may produce a similar appearance is an

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4. Holt, J. F.; Haight, C., and Hodges, F. J.: Congenital Atresia of the Esophagus and Tracheo-Esophageal Fistula, Radiology **47**:457-470, 1946.

5. O'Bannon, R. P.: Congenital Partial Atresia of the Esophagus Associated with Congenital Diverticulum of the Esophagus, Radiology **47**:471-477, 1946.

6. Davis, M. M.: Congenital Atresia of the Esophagus, Canad. M. A. J. **56**:539-541, 1947.

7. Ladd, W. E., and Swenson, O.: Esophageal Atresia and Tracheo-Esophageal Fistula, Ann. Surg. **125**:23-40, 1947.

8. White, M. L., Jr., and Birdsong, M.: Congenital Esophageal Atresia with Tracheo-Esophageal Fistula, Surgery **20**:548-557, 1946.

9. Eliason, E. L., and Welty, R. F.: Spontaneous Rupture of the Esophagus, Surg., Gynec. & Obst. **83**:234-238, 1946.

10. Frink, N. W.: Spontaneous Rupture of the Esophagus: Report of a Case with Recovery, J. Thoracic Surg. **16**:291-297, 1947.

11. Hennell, H.: Perforation of Esophageal Foreign Body into Lung: Putrid Pulmonary Abscess; Case Report, J. Mt. Sinai Hosp. **13**:203-204, 1946.

12. Lascano, E. F., and Señorans, A. J.: Fistula esofagico—aortica infeccioso, consecutiva a ura herida esofagico por cuerpo extrano, Arch agent. de enferm. d. ap. digest. y de la nutricion **21**:209-217, 1946.

13. Paul, W. D., and Antes, E. H.: Perforation of the Esophagus Caused by Flexible Gastroscope, Rev. Gastroenterol. **13**:23-25, 1946.

14. Johnstone, A. S.: Foreign Bodies in the Esophagus, Brit. J. Radiol. **20**:41-42, 1947.

abscess in the paraesophageal tissues, usually differentiated by the presence of a fluid level.

Stricture.—Three patients with benign strictures of the esophagus were treated successfully by esophagectomy and eophagogastric anastomosis performed in one stage.[15]

Diverticula.—Janes [16] describes 6 cases of pulsion diverticula of the lower part of the esophagus; the patients, 5 men and 1 woman, were from 41 to 59 years of age. The chief symptoms were dysphagia, pain, vomiting and loss of weight.

Cardiospasm.—The most effective method of treatment of cardiospasm, according to Vinson,[17] consists in stretching the cardia by means of large esophageal sounds or a hydrostatic dilator passed over a previously swallowed silk thread. Patients who have slight dilatation above the point of obstruction and in whom severe pain is a prominent symptom are more resistant to treatment than those with marked dilatation and angulation of the esophagus. Grimson and others [18] found a definite change in the size of the esophagus after cardioplasty in 8 of 9 cases; in 4 the esophagus gradually decreased to normal seven, thirty-four, thirty-seven and fifty-three months respectively after operation, in 2 it was almost normal at three and eleven months and in 2 it was significantly reduced in size at ten days and three months. One patient obtained no relief of obstruction, and there was no decrease in the size of the esophagus. Satisfactory results in the treatment of cardiospasm by esophagogastrostomy are reported also by Bell [19] in 8 of 10 cases; 2 patients required a subsequent operation. Schiebel [20] records good results in 4 cases of cardiospasm similarly treated and observed for six to thirty-five months. The experience of the reviewers is in accord with the observations of Vinson that the vast majority of patients with cardiospasm are completely relieved by mechanical dilation of the cardia and that surgical intervention is required for only a few.

Peptic Ulcer.—Morton and Brunschwig [21] report an instructive case in which peptic ulcer of the esophagus was present in a 65 year old wom-

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15. Sweet, R. H.: Subtotal Esophagectomy with High Intrathoracic Esophagogastric Anastomosis in the Treatment of Extensive Cicatricial Obliteration of the Esophagus, Surg., Gynec. & Obst. **83**:417-427, 1946.

16. Janes, R. M.: Diverticula of the Lower Thoracic Esophagus, Ann. Surg. **124**:637-652, 1946.

17. Vinson, P. P.: Diagnosis and Treatment of Cardiospasm, South. M. J. **40**:387-392, 1947.

18. Grimson, K. S.; Reeves, R. J.; Trent, J. C., and Wilson, A. D.: The Treatment of Patients with Achalasia by Esophagogastrostomy, Surgery **20**:90-95, 1946.

19. Bell, G. G.: The Treatment of Cardiospasm by Esophagogastrostomy, Surgery **20**:104-116, 1946.

20. Schiebel H. M.: Treatment of Esophageal Achalasia or Cardiospasm, Surgery **20**:558-570, 1946.

21. Morton, D. R., and Brunschwig, A.: Peptic Ulcer of the Esophagus: Report of a Patient with Ten Year Follow-Up, Gastroenterology **7**:314-319, 1946.

an observed for a period of ten years. The original sysmptoms consisted of postprandial epigastric burning relieved by alkalis and a bland diet, vomiting associated with substernal pain, increasing dysphagia and a loss of weight of 45 pounds (25 Kg.). Roentgen study revealed a 3 to 4 mm. irregular narrowing of the esophagus at the level of the seventh thoracic vertebra; the diameter was 3 to 4 mm. in the 10 cm. involved. The narrowing was not affected by inhalation of amyl nitrite. Esophagoscopy demonstrated a narrowing in the midportion of the esophagus and a well demarcated ulcer on the right lateral wall surrounded by a granular friable mucosa. Three biopsies revealed chronic ulceration. Gastrostomy utilizing a Pezzer catheter was performed, after which the patient gained weight and strength. She returned ten years later because of episodes of vomiting of blood for the preceding five months. Roentgen studies revealed the same constriction in the esophagus, somewhat less irregular, and a crater 3 mm. in diameter in the duodenal bulb. Esophagoscopy demonstrated a fibrous constriction at the site of the old lesion, which prevented passage of the instrument; however a no. 20 bougie was passed with little resistance. Feedings of milk and cream were given through the gastrostomy opening. The patient improved rapidly and was discharged in good condition.

Cardioesophageal Relaxation.—Cardioesophageal relaxation, according to Neuhauser and Berenberg,[22] is an infrequent but important cause of vomiting in the newborn. The diagnosis is suggested by the observation of persistent regurgitation which is alleviated by placing the patient in the erect position. Fluoroscopic examination demonstrates retrograde filling of the esophagus during inspiration or increase in intra-abdominal pressure, with persistant relaxation of the esophageal hiatus.

Scleroderma.—In a carefully studied case of scleroderma Goetz[23] noted roentgenologically a dilatation of the middle third and a narrowing of the lower third of the esophagus, esophageal ulceration, lack of peristalsis and stasis in the duodenum, dilatation of individual loops of the small intestine and extreme narrowing of the large bowel. Autopsy revealed involvement of all these areas.

Carcinoma.—Three cases of carcinoma of the esophagus are described, illustrating some of the problems associated with the disease.[24]

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22. Neuhauser, E. B. D., and Berenberg, W.: Cardio-Esophageal Relaxation as a Cause of Vomiting in Infants, Radiology **48**:480-483, 1947.

23. Goetz, R. H.: The Pathology of Progressive Systemic Sclerosis (Generalized Scleroderma), with Special Reference to Changes in Viscera, Clin. Proc. **4**:337-392, 1945.

24. Puppel, I. D.: Early Diagnosis in Radical Resection of Carcinoma of the Lower Esophagus, Am. J. Surg. **73**:695-699, 1947.

The number of successful resections continues to increase. Garlock [25] describes a new technic of combined abdominothoracic approach; Sweet [26] prefers the transthoracic method, with incision of the diaphragm. Lewis [27] performs a combined abdominal and thoracic operation in one or two stages. The abdominal portion consists of mobilization of the upper half of the stomach and a Witzel jejunostomy performed through a left paramedian incision. The thorax is opened on the right side, the esophagus freed and the stomach drawn through a widened hiatus. The stomach is anchored by suturing to the anterior cut edge of the mediastinal pleura, permitting end to side esophagogastrostomy without tension on the suture line. Of 7 patients subjected to this procedure, 5 recovered immediately.

Thirteen patients were operated on through a transthoracic approach for lesions of the lower part of the esophagus and of the cardiac end of the stomach; 12 had carcinoma and 1 an inflammatory lesion.[28] Resection of the lower end of the esophagus and of portions of the stomach was feasible in 7 patients. Of these, 1 died after nine months of metastasis after obtaining temporary relief. Another was known to have metastasis six months after operation and is presumed dead. Four patients are well from six months to more than a year after operation. One man had gained 31 pounds (14 Kg.) eleven months after operation. Another patient is reported to be convalescing.

Carter and McGrath [29] prefer the transthoracic approach to the transabdominal route because of a wider exposure, easier access and easier removal of regional lymph nodes. Indications for this procedure are carcinoma of the cardiac portion of stomach, carcinoma of the lower two thirds of the esophagus, benign stricture, diverticula in the lower third of the esophagus and chronic ulcer of the cardiac end of the stomach. Jejunostomy, performed under local anesthesia as a preliminary procedure, aids in the restoration of nutritional balance and also affords an opportunity for exploration of the entire upper area of the abdomen for evidence of metastasis. In forty-two major esophageal operations

25. Garlock, J. H.: Combined Abdominothoracic Approach for Carcinoma of Cardia and Lower Esophagus, Surg., Gynec. & Obst. **83**:737-741, 1946.

26. Sweet, R. H.: Carcinoma of the Mid-Thoracic Esophagus: Its Treatment by Radical Resection and High Intrathoracic Esophagogastric Anastomosis, Ann. Surg. **124**:653-666, 1946.

27. Lewis, I.: The Surgical Treatment of Carcinoma of the Esophagus, with Special Reference to a New Operation for Growths of the Middle Third, Brit. J. Surg. **34**:18-31, 1946.

28. Nagel, G. W., and Menke, J. F.: Transthoracic Operations for Neoplasms of the Esophagus and Stomach, Surg., Gynec. & Obst. **83**:657-666, 1946.

29. Carter, B. N., and McGrath, E. J.: Esophagogastrostomy for Lesions of the Upper End of the Stomach and Lower End of Esophagus, S. Clin. North America **26**:1125-1139, 1946.

by Kay the mortality rate was 2.4 per cent.[30] Humphrey[31] discusses the surgical treatment of 70 patients with carcinoma of the esophagus. Radical resection of the tumor was carried out in 33 cases, with an operative mortality rate of approximately 50 per cent. Rienhoff[32] describes 3 patients with a lye stricture, carcinoma at the level of the aortic arch and achalasia of the esophagus respectively who were successfully treated by the intrathoracic transplantation of the jejunum as a substitute for the esophagus. Favorable results are reported in the treatment of 2 patients with squamous cell carcinoma of the esophagus with a depth dose of 4,000 r administered over a period of four weeks.[33]

Leiomyomas.—Thirty-two of forty-four benign esophageal tumors found in 7,459 postmortem examinations performed at the Mayo Clinic were leiomyomas.[34] The authors recommend surgical removal of all such tumors because of the potential danger of malignant transformation.

Stomach

Gastric Secretion.—Forsgren[35] measured gastric secretion by Ewald test meals at 8:00 a.m., 1:00 p.m. and 6:00 p.m. of the same day in 557 patients with tuberculosis. The values for acidity remained approximately the same in 191 cases; considerable variation was noted throughout the day in the remaining 366 cases. In general, there was a tendency for acidity to decrease later in the day. The author believes that at least two test meals should be given, one on a fasting stomach in the morning and another later in the day, if an accurate appraisal of gastric secretory function is to be obtained. Observations on his own gastric secretory activity from 1925 to 1929 and from 1942 to 1944 by Hoelzel[36] disclosed a slight decrease in acidity and a decrease of approximately 50 per cent in the volume of gastric secretion during the nineteen year period. The average gastric acidity increased after restriction of protein and decreased when the intake of protein was augmented. Emotional stress was accompanied with a decided increase in acidity, as revealed by routine single daily determinations. The initial daily acidity, determined within a half hour after rising, was usually higher than the average of five to nine determinations made throughout the day.

30. Kay, E. B.: Surgical Lesions of the Esophagus Seen in an Army Thoracic Surgery Center, J. Thoracic Surg. **16**:207-214, 1947.

31. Humphrey, G. H.: An Approach to Resections of the Esophagus and Gastric Cardia, Ann. Surg. **124**:288-300, 1946.

32. Rienhoff, W. F., Jr.: Intrathoracic Esophagojejunostomy for Lesions of the Upper Third of the Esophagus, South. M. J. **39**:928-940, 1946.

33. Borak, J.: Radiation Therapy of Cancer of the Esophagus, Am. J. Digest Dis. **13**:249-252, 1946.

34. Calmenson, M., and Clagett, O. T.: Surgical Removal of Leiomyomas of the Esophagus, Am. J. Surg. **72**:745-747, 1946.

35. Forsgren, E.: To What Degree Does Gastric Acidity Show a Tendency to Rise or Fall During the Day? Acta med. Scandinav. **128**:281-288, 1947.

36. Hoelzel, F.: The Fasting Gastric Contents as an Index of Gastric Functioning, Am. J. Digest Dis. **13**:284-290, 1946.

Necheles [37] suggests that the increased gastric motility after burns in dogs may be due to two separate mechanisms, i.e., cholinergic and histaminic. Relatively large doses of atropine did not affect the augmented gastric secretion of the dog's stomach after burns. Obrink [38] states that the histamine concentration in the blood must be maintained at a constant level if a stimulating effect is to result. Such a constant level is reached only by slow continuous intravenous administration. In a Heidenhain pouch dog the gastric juice appears within four to six minutes after intravenous injection, but it does not reach a steady rate before twenty to thirty minutes; subsequently, an almost constant level can be maintained for hours.

Ihre [39] studied the gastric secretory response to histamine in a series of 264 patients, including 204 with duodenal ulcer (153 men and 51 women) and 60 with gastric ulcer (41 men and 19 women), utilizing a single tube and continuous suction of the stomach. The data are compared with results in 18 normal men and in 15 normal women. The volume of secretion was higher in men than in women of the group with duodenal ulcer. The values for men with gastric ulcer were higher than those for women, but the differences were not as marked. In the normal group there was no difference between the two sexes. The mean volumes of secretion in the group with duodenal ulcer exceeded those for patients with gastric ulcer and for normal persons. The values in men with gastric ulcer exceeded those in normal men. Hypersecretion (defined as a secretion volume of more than 180 cc. per sixty minutes) was found in 77 cases and more often in men than in women. The maximum acidity in any of the three twenty minute samples was of less significance than the volume of secretion inasmuch as the mean for normal persons was higher than that for patients with duodenal ulcer. A comparison between the histamine tests and the gastroscopic findings demonstrated that acidity values below 90 to 100 milliequivalents at a secretion volume of at least 50 cc. per sixty minutes indicate the presence of chronic gastritis. Acidity values above 100 milliequivalents, on the other hand, do not exclude the diagnosis of gastritis. Values up to 130 or 140 milliequivalents are considered indicative of a normal gastric mucosa.

The concentration of hydrochloric acid and the total volume of histamine-stimulated secretion were not significantly reduced by administration of "benadryl hydrochloride." [40]

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37. Necheles, H.; Prescott, E., and Olson, W. H.: The Effect of Atropine on the Gastric Secretion Following Thermal Trauma, Surgery **20**:382-384, 1946.

38. Obrink, K. G.: Some Relations in Gastric Stimulation by Intravenous Injection of Histamine, Acta physiol. Scandinav. **12**:213-218, 1946.

39. Ihre, B. J. E.: Studies in Gastric Secretion with an Improved Histamine Test, Acta med. Scandinav. **128**:322-340, 1947.

(*Footnotes continued on next page.*)

Musick and his associates,[41] confirming Ivy's work, found that caffeine stimulated secretion of hydrochloric acid in 10 apparently normal persons and produced an excessive prolonged secretory response in 25 patients with active duodenal and gastric ulcer.

The intravenous administration of moderate doses of quinine sulfate (0.2 to 0.3 Gm. to dogs weighing 10 to 15 Kg.) or of quinacrine hydrochloride (0.05 to 0.1 Gm. to dogs weighing 8 to 12 Kg.) markedly diminished the gastric secretion produced by rhythmic vagal stimulation;[42] small or moderate doses of quinine or of quinacrine hydrochloride did not affect histamine secretion.

In 56 patients the gastric free acidity was higher after graduated doses of protein hydrolysate than it was after an Ewald test meal, from which Rossien [43] concludes that the preparation is not an effective antacid.

The effects of vagotomy on secretion and motility of the stomach were studied in 10 dogs for periods of ten to fifty-seven months;[44] a reduction in secretion occurred in 9 of the 10. The response to histamine was permanently decreased during the period of observation. In most cases a gradual increase in the response to test meals was observed six months after vagus section; the secretion did not reach preoperative levels, however, and again decreased after a few years. Peptone added to test meals failed to stimulate acid secretion. This together with the observation that the histamine response was diminished led to the deduction that not only was the psychic phase of secretion lost but also the activity of the secretory mechanism of the stomach itself was reduced. The effect on motility was inconstant and variable; in general, motility tended to return to normal after variable periods. Vomiting or diarrhea or both, with loss of weight despite normal appetites, occurred in 4 dogs. Restoration of secretion was not due to regeneration of the vagi or to splanchnic innervation.

Wolf and Andrus [45] describe an important study of the effect of vagotomy on gastric function as observed through a fistula (gastrostomy)

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40. Moersch, R. U.; Rivers, A. B., and Morlock, C. G.: Some Results of the Gastric Secretory Response of Patients Having Duodenal Ulcer Noted During the Administration of Benadryl, Gastroenterology **7**:91-99, 1946. McElin T., and Horton, B. T.: Clinical Observations on the Use of Benadryl; Its Effect on Histamine Induced Gastric Acidity in Man, ibid. **7**:100-107, 1946.

41. Musick, V. H.; Hopps, H. C.; Avey, H. T., and Hellbaum, A. A.: The Effect of Caffeine on Gastric Secretion, South. M. J. **39**:651-658, 1946.

42. Babkin, B. P., and Karp, D.: Effect of Quinine and Atabrine on Gastric Secretion Canad. M. A. J. **56**:137-141, 1947.

43. Rossien, A. X.: An Evaluation of the Antacid Activity of Protein Hydrolysate Using Graduated Doses in the Human Stomach, Am. J. Digest Dis. **14**:205-207, 1947.

44. Vanzant, F. R.: The Late Restoration of Gastric Acidity After Thoracic Vagotomy in the Dog, Gastroenterology **8**:768-773, 1947.

45. Wolf, S., and Andrus, W. DeW.: The Effect of Vagotomy on Gastric Function, Gastroenterology **8**:429-434, 1947.

necessitated by an esophageal neoplasm. Sensations of pain, pressure, heat and cold induced by the proper stimuli, were not affected by vagotomy. Vigorous motor activity was accompanied with hyperemia but not with an increased acidity. After vagotomy the mucous membrane was usually pale and spontaneous motor activity was not observed. However, mild hyperemia and engorgement appeared after a meal. Induced feelings of anger and resentment prior to vagotomy produced hyperemia, engorgement and hypermotility but no increased acidity. After vagotomy anger and resentment caused no observable changes in gastric function. Injection of "prostigmine" prior to vagotomy resulted in striking acceleration of motor activity and in hyperemia of the mucosa, without an increase in acid secretion. After vagotomy these effects were slight but still observable.

In a study of gastric secretion in the aged, Rafsky and Weingarten [46] found that of 47 apparently normal persons over 65 years of age, 53.2 per cent had 19 or less units of free hydrochloric acid after a bread and water test meal; achlorhydria was present in 17 per cent but not achylia gastrica, for milk-coagulating activity was present. Six patients, or 12.7 per cent, were found to have free acid values ranging from 50 to 90 clinical units. Rafsky and his co-workers [47] briefly review the conflicting evidence on the effect of thiamine deficiency on gastric acidity, present results of a study and conclude that it is questionable whether any causal relationship exists.

The chewing of gum temporarily reduced gastric acidity in 12 presumably healthy persons.[48]

Hypohysectomy is reported by Crafts and Walker [49] to have reduced the secretion in adult female rats from a control volume of 0.38 cc. to one of 0.23 cc.; the free acidity was lowered from 0.0037 to 0.0001 milliequivalents. Further studies of endocrine effects on gastric secretion would be interesting.

A simple, inexpensive and accurate method is presented for the measurement of pepsin and trypsin.[50] An improved method for the

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46. Rafsky, H. A., and Weingarten, M.: A Study of the Gastric Secretory Response in the Aged, Gastroenterology **8**:348-352, 1947.

47. Rafsky, H. A.; Lewman, B., and Jollife, N.: The Relationship of Gastric Acidity to Thiamine Excretion in the Aged, J. Lab. & Clin. Med. **32**:118-124, 1947.

48. Smith, C. S.; Wickoff, H. L., and Southard, M. E.: Some Effects of Gum Chewing on Gastric Acidity in Healthy Individuals, Am. J. Digest Dis. **13**:245-247, 1946.

49. Crafts, R. C., and Walker, B. S.: The Effects of Hypophysectomy on Gastric Acidity of Adult Female Rats, Endocrinology **40**:395-402, 1947.

50. Friedman, M. H. F.: A Simplified Procedure for the Determination of Pepsin and Trypsin Concentrations in Digestive Juices, Gastroenterology **8**:526-532, 1947.

measurement of total peptic activity of gastric juice is described by LeVeen.[51] Egg albumin is used as substrate, and a photoelectric colorimeter, used as a densimeter, is employed to determine the amount of albumin solution digested. A method of greater sensitivity utilizes purified bovine and human serum albumin. The author [52] believes that the values for total pepsin of gastric juice give no indication of the digestive action in vivo as modified by inhibitory substances and $_{p}H$. Total pepsin can be assayed only after high dilution of gastric juice, when it is completely freed from inhibitory peptones. Procedures are described whereby the amount of active pepsin, the percentage of pepsin inhibition and the active peptic power can be determined when they are used in combination with the test for total pepsin noted previously.

Brummer [53] states that the presence of achlorhydria is of indisputable value in the differential diagnosis between pernicious anemia and other macrocytic anemias. He believes that hydrochloric acid promotes the digestion of protein to some extent but apparently is not indispensable to it. Achlorhydria is not accompanied with disturbances in the motility of the stomach and the intestine or in the intestinal flora. Dyspeptic distress and a tendency to diarrhea are not more common in achlorhydric patients than in other persons. Therapeutic results supposedly obtained with hydrochloric acid do not prove that the latter is necessary for digestion, because the usual therapeutic doses have no effect on the reaction of the gastric contents. Thus achlorhydria is of no great importance from the standpoint of digestion or as a cause of digestive disturbances. The reviewers are in complete accord with these observations.

Brummer [54] presents a new method of determining the content of mucin in gastric juice. In this procedure the proteins are first precipitated with picric acid, the mucin then being precipitated from the filtrate with alcohol. The grade of turbidity thus obtained is used as a standard for the mucin content. In studies of 313 specimens obtained from 145 persons, 50 healthy and 95 suffering from various gastric disorders, the mucin content of the gastric juice varied from 0.15 to 1.5 per cent, with an average of approximately 0.5 per cent. The mucin content was slightly higher in the juice after a test meal than in the fasting juice. Histamine and insulin appeared to have no effect on the mucin content. No significant difference was found in the various gastric disorders. The mucin con-

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51. LeVeen, H. H.: Total Peptic Activity of Gastric Juice: A Method of Determination, Proc. Soc. Exper. Biol. & Med. **63**:254-259, 1946.

52. LeVeen, H. H.: Active Pepsin Fraction, Resting Peptic Activity, and Percentage of Pepsin Inhibition in Gastric Juice, Proc. Soc. Exper. Biol. & Med. **63**:259-263, 1946.

53. Brummer, P.: Clinical Significance of Achlorhydria, Ann. med. int. Fenniae **36**:9, 1947.

54. Brummer, P.: On the Mucin Content of Gastric Juice, Acta med. Scandinav. **126**:384-392, 1946.

tent of the gastric juice of patients with peptic ulcer and in those with gastritis was within the normal range.

No statistically significant stimulation of mucus secretion by the pyloric mucosa was observed after injections of pilocarpine.[55]

Repeated application of a 5 per cent eugenol-water emulsion to the pouch mucosa of a fasting dog results in progressive denudation of the protective layer of columnar cells and of many of the neck chief cells in parts of the mucosa.[56] By the time the fourth application is made the mucous barrier is seriously impaired; the disturbance persists for at least three months. After the sixth application there is evidence of a considerable inflammatory reaction of the tissue.

Hollander and others[57] found a 1 per cent emulsion of mustard oil in water to be an unsatisfactory stimulus for gastric mucus secretion; it acts as an active mucosal irritant, inducing an inflammatory reaction as well as a mucoid response. The gastric secretion produced is pinkish and congeals quickly and is predominantly a serous transudate.

Gastric Motility and Absorption.—Van Liere[58] and his associates report that the addition of glucose to a standard test meal for 19 young men prolonged gastric emptying to a degree roughly proportional to the amount ingested. Twenty-five grams produced 21 per cent prolongation above the norm, 50 Gm. a 39 per cent prolongation and 75 Gm. a 51 per cent prolongation.

The amount of glucose emptied from the stomach was greater and the absorption smaller when large volumes of dilute solutions of dextrose were given than when small volumes of concentrated solutions were administered, the total amount of dextrose fed being constant.[59] With identical concentrations, greater absorption and emptying was observed when larger volumes were used. With identical volumes, greater absorption and emptying was observed from the more concentrated solutions.

Studies on gastric motility in 8 normal young men indicated that, within nutritionally reasonable limits, increasing the proportion of the calories

55. Ivy, J. S.: The Effect of Pilocarpine on Mucus Secretion by the Pyloric Mucosa, Gastroenterology **7**:224-230, 1946.

56. Hollander, F.; Sonnenblick, B. P., and Sober, H. A.: Experimental Impairment of the Gastric Mucous Barrier in Dogs, J. Nat. Cancer Inst. **7**:361-364, 1947.

57. Hollander, F.; Lauber, F. U., and Stein, J.: Some Characteristics of Gastric Secretion Induced by Mustard Oil Suspension, Am. J. Physiol. **149**:724-731, 1947.

58. Van Liere, E. J.; Northup, D. W., and Stickney, J. C.: The Effect of Glucose on the Motility of the Stomach and Small Intestine, Gastroenterology **7**:218-223, 1946.

59. Birchall, E. F.; Fenton, P. F., and Pierce, H. B.: Gastric Emptying and Intestinal Absorption of Dextrose Solutions, Am. J. Physiol. **146**:610-612, 1946.

in the test meal from fat, protein or carbohydrate did not significantly alter gastric motility.[60]

According to Annegers and Ivy,[61] a person with a given volume of gastric contents has a reliably constant gastric shadow area when the stomach is outlined with a small amount of barium. This area varies with changes in the gastric content. A method based on these observations has been devised whereby variations in the rate of gastric evacuation in a given person may be determined by the measurement of the shadow areas with a planimeter after variation of the test meal or administration of drugs. Evaluation of the rate of gastric emptying by means of fluoroscopic examination, gastric intubation and determination of blood concentrations of test drugs indicated to Lolli and Smith [62] that effervescent mixtures decrease the emptying time of the stomach.

Harris and his associates [63] found that fat in the intestine inhibits gastric motility induced by distention in both vagally innervated and vagally denervated stomachs. Intravenously administered urogastrone and enterogastrone extracts inhibit the distention-induced motility of the vagally innervated stomach but either have no effect on the vagally denervated stomach or stimulate motility in it.

By means of electrodes placed in the mucosa and submucosa of the stomach, potential differences were studied under various conditions by Rehm.[64] Changes in potential noted after the injection of histamine and thiocyanate were due to changes in the potential difference between submucosa and mucosa; alcohol when applied directly to the submucosa created no significant changes in potential between mucosa and submucosa. It is concluded that the electromotive force originates in the secretory portion of the stomach.

Gastric Cytology.—A new technic for studying the cytologic elements in gastric contents is described, in which smears are stained with toluidine blue;[65] the columnar cells are better preserved by this procedure.

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60. Henschel, A.; Keys, A.; Sturgeon, A. M., and Taylor, H. L.: The Influence of Test Meal Composition on Gastric Emptying in Man, Am. J. Physiol. **149**:107-111, 1947.

61. Annegers, J. H., and Ivy, A. C.: A Method for Determining the Effect of Various Agents on Gastric Evacuation in Man, Gastroenterology **8**:711-716, 1947.

62. Lolli, G., and Smith, R.: Effervescent Mixtures as Adjuvants to the Rapid Absorption of Ingested Drugs, New England Med. **235**:80-84, 1946.

63. Harris, S. C.; Grossman, M. I., and Ivy, A. C.: The Role of the Vagus Nerves in the Inhibition of Gastric Motility by Fat and by Intestinal and Urinary Extracts, Am. J. Physiol. **148**:338-343, 1947.

64. Rehm, W. S.: Evidence That the Major Portion of the Gastric Potential Originates Between the Submucosa and Mucosa, Am. J. Physiol. **147**:69-77, 1946.

65. Hollander, F.; Hess, M., and Sober, H. A.: New Technique for Studying the Cytology of Gastric Aspirates in Man, J. Nat. Cancer Inst. **7**:365-366, 1947.

In a two hundred page article containing numerous tables and illustrations Tomenius [66] attempts to correlate gastroscopic findings with studies of the sediment of gastric juice. With the use of a four channel gastric tube, secretions were aspirated from the esophagus, stomach and duodenum through three of the channels, and through the fourth an isotonic (1.3 per cent) solution of sodium bicarbonate was introduced into the stomach by continuous flow. Aspirations were made by an apparatus maintaining a negative pressure subject to the operator's control. Examination of the sediment in 26 "normals" disclosed the presence of squamous cells in at least 47 per cent of the total number of samples; large pigmented cells (contamination from the respiratory passages) occurred in 7.3 per cent, red blood corpuscles in 3.8 per cent, columnar epithelium in 3 per cent and leukocytes in only 1.7 per cent. Study of 16 cases of gastritis (excluding atrophy) disclosed an increased number of cells, especially leukocytes. The cytologic picture in the 7 cases of atrophic gastritis and in the cases of peptic ulcer resembled that in normal cases. An increase in leukocytes and in red blood corpuscles was noted in the patients with cancer of the body of the stomach. In cases of cancer of the cardia there was an increase in squamous cells but not in leukocytes.

Varying results are reported on the accuracy of cytologic study of the gastric contents as an indication of gastric disease. In one investigation the gastroscopic findings were correlated with the cytologic changes in the gastric juice in 68 patients with gastritis and gastric ulcer.[67] A relationship was noted between the increase in the number of the leukocytes in the gastric juice and the degree of alteration in the mucosa. On the other hand, a study of the cells in the gastric secretion of normal persons and of patients with duodenal ulcer, gastric ulcer and gastritis revealed no correlation between the number of cells and the various diseases.[68]

Effect of Drugs, Nausea and Emotions.—Wolf and Wolff,[69] studying the action of drugs and various chemical agents on the gastric mucosa and the gastric function in man, found that while alkalis, acids, condiments and drugs such as digitalis, aminophylline, ammonium chloride, ferrous sulfate, and the sulfonamide compounds produced irritation when applied locally to the skin no irritation resulted from their application to the gastric mucosa. During the vasoconstriction produced by epinephrine and "benadryl hydrochloride," the mucosa was resistant to scratching from a dry gauze or to a blow from a blunt glass rod. Local application

66. Tomenius, J. H.: A Study on the Gastric Sediment, Acta med. Scandinav. 1947, supp. 189, pp. 1-402.

67. von Kapp, H.: Die diagnostische Bedeutung der Zelluntersuchung des Magensaftes, Gastroenterologia **71**:289-294, 1946.

68. Altamira, J. del V., and Rennella, M.: Citologia del contenido gastrico en condiciones normales y patologicas, Rev. med. de Cordoba **35**:8-22, 1947.

69. Wolf, S., and Wolff, H. G.: Action of Drugs and Various Chemical Agents on the Gastric Mucosa and Gastric Function in Man, New York State J. Med. **46**:2509-2512, 1946.

of a 0.5 per cent solution of copper sulfate produced edema, engorgement and minute hemorrhages in the mucosa; under these conditions the mucosa was less resistant and easily damaged by mechanical injury. Peripherally acting emetics induced nausea only after reaching the duodenum.

The occurrence of nausea among soldiers overseas was found to accompany emotional reactions to adverse life situations.[70] Fear, despondency or a feeling of defeat were accompanied with a desire to reject the offending situation. Fluoroscopic observations on the barium-filled stomach and intragastric balloon studies tended to show that vomiting was brought on by the force of contraction of the diaphragmatic and abdominal musculature rather than by activity of the stomach. Nausea was accompanied with a decrease in the contractile state of the stomach and by cessation of motor activity.

The authors describe new experiments confirming earlier observations indicating the occurrence of two types of disturbances in the stomach in response to threatening situations.[71] These patterns are characterized by either overfunctioning or underfunctioning of the organ. Gastric hyperactivity was found to be frequently associated with heartburn and gnawing epigastric pain, characteristically more intense during periods when the stomach was empty and usually relieved by the taking of food, milk or alkali. Gastric hypoactivity was found to be accompanied with feelings of fulness in the epigastrium and nausea. The principal difference between the emotional reactions accompanying gastric hyperfunction on the one hand and hypofunction on the other appears to be in whether or not the subject accepts defeat in the adverse situation. The person whose stomach is hyperactive is physiologically prepared for food whether or not he has an appetite; he is angry, preparing for either fight or flight. The person whose stomach is hypoactive is not accepting the challenge of the situational threat. He considers himself defeated; the nausea expresses his rejection of the situation.

Uropepsin.—Uropepsin, a pepsin-like enzyme, in urine has been studied chiefly by German physiologists and clinicians. Bucher [72] undertook to verify its existence and stability and to confirm and evaluate some of the factors reported to produce variations in its excretion in normal persons. Assay was carried out by measuring the amount of tyrasine released from the digestive action of urine on a hemoglobin substrate. The

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70. Wolf, S.: Observations on the Occurrence of Nausea Among Combat Soldiers, Gastroenterology **8**:15-18, 1947.

71. Wolf, S., and Wolff, H. G.: An Experimental Study of Changes in Gastric Function in Response to Varying Life Experiences, Rev. Gastroenterol. **14**:419-426, 1947.

72. Bucher, G. R.: Uropepsin: A Review of the Literature and Report of Some Experimental Findings, Gastroenterology **8**:627-647, 1947.

p_H range for optimal digestion of hemoglobin substrate by uropepsin is tentatively 2.0 to 3.4. Uropepsin, regardless of the p_H of the urine, is stable for up to fifteen days if refrigerated after collection under toluol. Uropepsin, in contrast to pepsin, occurs in alkaline urine. Diet may significantly alter uropepsin output; a doubled protein intake markedly increases the output whereas restriction of protein reduces it. A milk diet containing amounts of protein similar to those in diets for the control group produced no appreciable change in uropepsin excretion. The output of uropepsin was distinctly higher during periods of emotional stress.

Diaphragmatic Hernia.—Among 53 patients with paraesophageal hiatus hernia women predominated in the proportion of 3 to 2; only 3 were under 50 years of age.[73] The chief symptom was distress after eating, especially after heavy meals. Occasionally there was pain in the epigastrium or behind the lower portion of the sternum. Pain was sometimes precipitated or aggravated by lying down, while relief followed rising or walking. In 2 cases there was moderate retrosternal pain referred to the left shoulder and arm, suggesting angina. Severe and prolonged hemorrhage occurred in 3 instances. Severe pain, frequent vomiting, anemia or interference with respiration or circulation are considered indications for surgical treatment. Satisfactory results were obtained in 14 of 16 cases in which surgical treatment was given. Codounis[74] reviews the subject in detail and emphasizes the desirability of surgical intervention in cases in which there is severe anemia.

Volvulus.—Three cases of detorsion of a chronic gastric volvulus during roentgen examination are described.[75]

Diverticula.—Ferguson and Cameron[76] present a technic for the treatment of diverticula consisting of invagination of the diverticulum, with suture of the muscular ring. This procedure was applied successfully in 5 cases, in 2 of which there was diverticula of the stomach and in 3 diverticula of the duodenum.

Gastroscopy.—A simultaneous roentgenologic and gastroscopic examination was performed on 3 patients. Gastroscopy was performed in a routine manner, and roentgenograms were taken in the left lateral and anterior projections which recorded the position of the gastroscope when important landmarks were seen through the instrument.[77] It was

73. Trueman, K. R.: Diagnosis and Treatment of Para-Esophageal Hiatus Hernia, Canad. M. A. J. **56**:149-153, 1947.

74. Codounis, A.: Contribution a l'étude des syndromes anemiques des hernies diaphragmatiques, Acta gastro-enterol, belg. **10**:179, 1947.

75. Chaumerliac, H., and Duperrier-Nigon: Detorsion de trois cas de volvulus chronique de l'estomac observée au cours de l'examen radiologique, Acta gastroenterol. belg. **9**:249-253, 1946.

76. Ferguson, L. K., and Cameron, C. S.: Diverticula of the Stomach and Duodenum, Surg. Gynec. & Obst. **84**:292-300, 1947.

77. Ould, C. L., and Dailey, M. E.: Simultaneous Radiographic and Gastroscopic Examination of the Stomach, Radiology **48**:8-14, 1947.

calculated that 1,500 to 2,000 cc. of air may be introduced into the stomach in a routine gasstroscopy. The roentgenograms demonstrated a considerable amount of air distending not only the stomach but also the duodenum and the upper part of the small intestine. The air in the small bowel, increasing as the examination progresses, pushes the stomach anteriorly and may distort its lower pole. These alterations may explain the failure of inexperienced gastroscopists to visualize the pylorus. Passage of the instrument beyond the cardia was along the posterior wall in 1 instance, always contacting the mucosa; in another it was carried through the lumen and did not impinge on the posterior wall until the lower third of the stomach was reached; in the latter instance, the posterior blind area was smaller than in the first instance.

Fluorescein proved to be a helpful adjunct in the gastroscopic visualization of a gastric ulcer in 4 cases.[78] The procedure consists in the administration of 10 cc. of the dye through the Ewald tube after emptying of the stomach; the ulcers assume a greenish fluoreseence and thus are more easily detected.

Moersch [79] comprehensively reviews the value of gastroscopy in the diagnosis of various gastric diseases. Similar discussions are presented by Monat and Thompson [80] and by Jones.[81] The group for whom gastroscopic examination is indicated in the army, as defined by Chamberlin,[82] consists of patients with typical intragastric disease who could be used for teaching purposes, those with obscure or doubtful lesions (for the purpose of more accurate diagnosis) and those without roentgenologically demonstrable disease (in order to make a diagnosis).

Benedict [83] analyzes the limitations of gastroscopy and roentgenology in the differential diagnosis of benign and malignant lesions of the stomach on the basis of a series of 53 patients with proved gastric disease, including 19 with carcinoma, 21 with benign gastric ulcer, 2 with jejunal ulcer, 5 with gastritis, 2 with benign tumors, 1 with lymphoma, 1 with a posterior gastroenterostomy stoma and 2 with a normal stomach. In 19

78. Robinson, H. M.: Fluorescein: An Aid in Gastroscopy, Rev. Gastroenterology **13**:303-305, 1946.

79. Moersch, H. J.: The Value of Gastroscopy in the Diagnosis of Gastric Disease, M. Clin. North America **30**:903-911, 1946.

80. Monat, H. A., and Thompson, C. M.: Evaluation of Gastroscopic, Roentgen, Sigmoidoscopic and Laboratory Procedures in Five Hundred Gastrointestinal Cases, Rev. Gastroenterol. **13**:19-21, 1946.

81. Jones, C. M.: The Value of Gastroscopy to the Clinician, Gastroenterology **8**:278-283, 1947.

82. Chamberlin, D. T.: Criteria for Gastroscopic Examination in the Army, Gastroenterology **8**:131-134, 1947.

83. Benedict, E. B.: The Limitations of Roentgenology and Gastroscopy in the Diagnosis of Diseases of the Stomach: An Analysis of Fifty-Three Proven Cases, Gastroenterology **8**:251-277, 1947.

cases of proved carcinoma the roentgenologic and gastroscopic diagnoses were both correct in 10 instances. In 1 case a malignant ulcer was interpreted as benign by both methods. In 1 case the disease was doubtfully malignant as judged by the roentgenologic evidence and appeared benign at gastroscopy. Gastroscopy failed to visualize an ulcerating neoplasm in another patient. Gastroscopy revealed the true nature of the lesion in 6 cases in which the roentgenologic diagnosis was doubtful. Of 21 instances of benign gastric ulcer, the disease was correctly diagnosed in 8 by both the radiologist and the gastroscopist; both procedures resulted in incorrect diagnosis in 5 cases. Gastroscopy failed to visualize the lesion in 5 cases, and in 1 an erroneous diagnosis of malignancy was made. In 2 cases the gastroscopist diagnosed benign lesions previously interpreted as malignant on roentgenologic examination. It was difficult to correlate the roentgenologic, gastroscopic and pathologic findings in the 5 cases of gastritis. In summary, both methods resulted in correct diagnosis in 21 cases and in incorrect diagnosis in 8. Gastroscopy was more correct in 13 cases and roentgen examination more correct in 11. In 8 of the latter visualization was inadequate because of mechanical limitations. It is concluded and emphasized that the two methods are mutually helpful and that greater diagnostic accuracy is obtained when both are utilized.

Experimental Gastritis.—Antral and fundic lesions were produced in rats by the use of diets deficient in calcium and vitamin B. Alterations in the mucosal vessels were demonstrated by injections of india ink. The antral lesions corresponded to changes found in human antral gastritis, and the fundic lesions were similar to hemorrhagic erosions in man.[84]

Symptoms in Patients with Gastritis.—One hundred and ten consecutive and unselected patients complaining of "chronic dyspepsia" were studied by clinical, roentgenologic, psychiatric and gastroscopic examination.[85] Fifty-nine per cent had a normal gastric mucosa. In 41 per cent there were mild to moderate abnormalities, consisting of redness, exudation and edema. There was no correlation between the appearance of the mucosa and the symptomatology, the symptoms being the same whether or not the mucosa was normal. Approximately 85 per cent of the total and 75 per cent of those with gastroscopic abnormalities had psychoneurosis. The authors interpret the gastroscopic changes as evidence of functional circulatory alterations resulting from nervous tension rather than as evidence of organic disease.

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84. Berg, B. N.: Vascular Changes in the Mucosa in Experimental Nutritional Gastritis, Gastroenterology **7**:340-354, 1946.

85. Halsted, J. A.; Schwartz, I. R.; Rosen, S. R.; Weinberg, H., and Wyman, S. M.: Correlated Gastroscopic and Psychiatric Studies of Soldiers with Chronic Non-Ulcerative Dyspepsia, Gastroenterology **7**:177-190, 1946.

One hundred and fifty records of patients with the gastroscopic diagnosis of gastritis, including the records of 50 cases each of atrophic, hypertrophic and superficial gastritis, were reviewed by Horner.[86] Approximately 80 per cent of each group described some form of epigastric distress. Pain was present in 80 per cent of the patients with hypertrophic gastritis, in 66 per cent of those with superficial gastritis and in none of the group with atrophic gastritis. In 71 per cent of the last group the chief symptom was "fulness" or "pressure." The taking of food or alkali provided relief from pain in half of the group with hypertrophic gastritis and in one fourth of the group with superficial gastritis. Nausea and vomiting were present in about one third of each group. Weight loss was most frequent (30 per cent) in the series with atrophic gastritis and was noted in only 12 per cent of each of the other two groups. The findings are interpreted as suggestive but not conclusive evidence that gastritis is directly concerned in the production of epigastric distress.

Fifty-eight patients with previously diagnosed functional gastrointestinal disease were subjected to gastroscopic study.[87] A diagnosis of gastritis was made in 25; it was hypertrophic in 11, atrophic in 7 and superficial in 7. In the remaining 33 the gastroscopic findings were normal. The clinical features in 25 of this group were compared with those in the "gastritis" group. Nausea, belching, bloating, anorexia and vomiting were the most common symptoms in both groups. Loss of weight exceeding 10 pounds (4.5 Kg.) had occurred in 7 of the group with gastritis. Epigastric tenderness was present in members of both groups. Gastric acidity varied widely and was unrelated to the presence or absence of gastritis. There was, however, a distinct tendency for the group with atrophic gastritis to secrete less acid than the others. Both groups were placed on essentially the same therapeutic regimen, namely a bland, low residue diet, with liver and vitamins, and avoidance of hot and cold foods, tobacco and alcohol. Each of the patients with gastritis admitted that they experienced at least a 50 per cent improvement, although 3 with chronic hypertrophic gastritis and 1 with atrophy showed no improvement on gastroscopy. Two with atrophic gastritis and 6 with superficial gastritis were rendered asymptomatic, and in 4 of the latter the gastritis apparently subsided. Of the group with functional gastric disease, none felt 50 per cent better, 7 were 25 per cent improved, 16 described no change and 10 were worse.

The varying interpretations drawn from these three studies are consistent with the experience of the reviewers. The evaluation of symptoms in patients with gastritis is often extremely difficult. Although chronic gastritis seems to be more prevalent in patients with discomfort

86. Horner, J. L.: The Symptomatology of Chronic Gastritis, Gastroenterology **8**:607-611, 1947.

87. Palmer, E. D.: The Chronic Gastritis Problem: Functional Upper Gastrointestinal Disease in Military Personnel and the Value of Establishing an Organic Basis for Diagnosis and Treatment, Gastroenterology **8**:743-753, 1947.

in the upper abdominal area, it is not infrequently encountered in patients with distress in the lower abdominal area or with complete absence of symptoms. Furthermore, the gastric mucosa may appear normal gastroscopically in persons with severe distress.

Large Gastric Rugae.—Ricketts, Kirsner and Palmer [88] direct attention to the fact that large but otherwise normal gastric rugae may roentgenologically simulate the appearance of neoplasm of the stomach. Gastroscopic examination in 3 cases demonstrated the benign nature of the rugae. The large pliable folds returned to normal size in 2 cases after insufflation of air and in the third case after subsidence of peristaltic activity. There was no evidence of gastritis as noted gastroscopically. A somewhat similar case, without gastroscopic observation, is reported by Maissa and Conteno.[89]

Hypertrophic Gastritis.—Two instances of hypertrophic gastritis roentgenologically simulating neoplasm of the stomach are reported;[90] the diagnoses were based on histologic examination.

Six well studied cases of giant hypertrophic gastritis, in 2 of which there was superimposed hyperplastic polyp formation, are described by Maimon and his associates.[91] The symptomatology varied from vague abdominal or epigastric distress to a syndrome simulating ulcer with or without vomiting. Differential diagnosis was difficult, attested by the fact that all the patients were operated on because of the possibility of neoplasm. Gastroscopically, anatomically and roentgenologically the gastric folds resembled the convolutions of the brain. The histologic changes consisted of redundancy of the mucosa and hypertrophy of glandular structures, cyst formation and metaplasia to the intestinal type of epithelium. The cells forming pepsinogen and acid were replaced by more primitive cells. Multiple polyps developed in 2 cases.

Pyloric obstruction occurred as a complication of chronic hypertrophic gastritis in a 53 year old man.[92]

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88. Ricketts, W. E.; Kirsner, J. B., and Palmer, W. L.: Large, Otherwise Normal Gastric Rugae Simulating Tumor of the Stomach, Gastroenterology **8**:123-130, 1947.

89. Maissa, P. A., and Centeno, A. M.: Imagenes pseudoneoplasicas por gastritia hypertropficas, Arch, argent. de Enferm. d ap. digest y de la nutricion **21**:199-208, 1946.

90. Bank, J.; Pearce, A. E., and Gilmore, J. H.: Hypertrophic Gastritis Simulating Neoplasm, Am. J. Digest Dis. **13**:344-346, 1946. Camena d'Almeida, P.: La biopsie de muqueuse gastrique sous controle gastroscopique, Acta gastro-enterol. belg. **9**:497-502, 1946.

91. Maimon, S. N.; Bartlett, J. P.; Humphreys, E. M., and Palmer, W. L.: Giant Hypertrophic Gastritis, Gastroenterology **8**:397-428, 1947.

92. Judd, E. S., and Moe, A. E.: Chronic Hypertrophic Gastritis Complicated by Obstruction: Report of Case, Proc. Staff Mee., Mayo Clin. **22**:241-249, 1947.

Atrophic Gastritis.—Moutier and Martin [93] report two interesting observations of chronic atrophic gastritis associated with multiple erosions. The lesions were characterized roentgenologically by small round niches similar to those produced by benign polyps but umbilicated at their apexes. The umbilicated appearance was clearly visualized gastroscopically.

Antral Gastritis.—The difficulty of differentiating between antral spasm and antral gastritis as well as between these two conditions and carcinoma is emphasized by Rennie.[94]

Congenital Pyloric Stenosis.—Donovan [95] summarizes his experience with 507 cases of congenital hypertrophic pyloric stenosis. The mortality rate from surgical intervention was 1.8 per cent for the entire series and 0.8 per cent for the last 245 cases (1937 to 1946). Additional observations on this entity are presented by Chene and Spriet,[96] Akin and Forbes [97] and Todd.[98]

Hypertrophic pyloric stenosis occurred in a man of 46 with a four year history of epigastric distress.[99] Operation revealed considerable hypertrophy of the entire pyloric sphincter, producing almost total obstruction; a partial gastric resection was performed. The pyloric musculature on cross section measured 1.5 cm. in thickness. No emotional factors of etiologic significance were encountered.

Pyloric stenosis in binovular twins [100] is reported as an exception to the rule that when one is affected the other will not be.

Two cases of congenital pyloric stenosis were observed in a family of 3 children; both patients were boys and were the first two offsprings in the family, suggesting a hereditary factor.[101]

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93. Moutier, F., and Martin, J.: Deux cas de gastrite varioliforme, Arch. d. mal. de l'app. digestif **36**:154-160, 1947.

94. Rennie, J. W. R.: Antral Gastritis and Spasm: Their Clinical and Surgical Significance, Ann. Surg. **124**:402-409, 1946.

95. Donovan, E. J.: Congenital Hypertrophic Pyloric Stenosis, Ann. Surg. **124**:708-715, 1946.

96. Chene, P., and Spriet, R.: Les stenoses hypertrophiques benignes du pylore chez l'adulte, Arch. d. mal. de l'app. digestif **35**:285-302, 1946.

97. Akin, J. T., Jr., and Forbes, G. B.: Congenital Hypertrophic Pyloric Stenosis, Surgery **21**:512-522, 1947.

98. Todd, R. M.: Review of One Hundred and Twelve Cases of Congenital Hypertrophic Pyloric Stenosis, Arch. Dis. Childhood **22**:75, 1947.

99. Vorhaus, M. G.: Hypertrophic Pyloric Stenosis in the Adult, Gastroenterology **7**:464-468, 1946.

100. Laubscher, J. H., and Smith, A. M.: Pyloric Stenosis in Twins: Review of the Literature and Report of a Case, Am. J. Dis. Child. **73**:334-341 (March) 1947.

101. Kaufman, B.: Congenital Pyloric Stenosis. Report of Two Cases in a Family of Three Children, Arch. Pediat. **64**:1-5, 1947.

In 9 infants with congenital hypertrophic pyloric stenosis, alkalosis was successfully ameliorated by the intravenous or subcutaneous injection of a solution of ammonium chloride in one-sixth molar concentration in isotonic solution of sodium chloride.[102] Toxic effects consisting of pallor, muscular twitchings and bradycardia were observed in only 1 patient, in whom the material was injected intravenously at an excessively rapid rate.

Pylorospasm.—Brackett [103] regards pylorospasm and intestinal colic as abnormalities of the motor mechanism of the digestive tract. He found that both could be controlled by reducing the volume of food and evoked by increasing the quantity of food.

Foreign Bodies.—Sharp-pointed foreign bodies swallowed into the stomach should be treated conservatively, according to Best,[104] with careful observation and repeated fluoroscopic or roentgenologic examination. Only occasionally will surgical intervention be needed. Indications for surgical treatment include the appearance of signs and symptoms of impending perforation or a twenty-four to forty-eight hour delay of the foreign body at any fixed point. Removal of metallic foreign bodies from the stomach by means of an alvico permanent magnet is discussed, and its successful application in 1 case is described.[105]

Silber and Epstein [106] utilize a fluoroscopically guided alvico magnet attached to a Levine tube inserted into a large caliber rubber tube. This assembly is passed into the stomach, with the magnet protruding slightly. When the foreign body is firmly attached to the magnet, both are withdrawn as far as necessary into the end of the rubber sheath by pulling on the inner tube. Thus protected, the foreign body moves easily through all narrow places and safely past the open air passages.

Gastroileostomy.—Twenty-two cases of gastroileostomy previously described in the literature are reviewed, and 3 new ones are presented.[107] The predominant symptoms were weight loss, diarrhea, pain and vomiting, sometimes fecal in type. Hemorrhage occurred in 3; ileal ulcer was present in 6 of the 22 cases previously reported. Roentgenologic exami-

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102. Forbes, G. B., and Erganian, J. A.: Parenteral Administration of Ammonium Chloride for Alkalosis of Congenital Hypertrophic Pyloric Stenosis., Am. J. Dis. Child. **7**:649-660 (Dec.) 1946.

103. Brackett, A. S.: The Alleviation of Pylorospasm and Colic in Infants by Reducing the Volume of the Food Intake Per Feeding, Yale J. Biol. & Med. **19**:155-169, 1946.

104. Best, R. R.: Management of Sharp Pointed Foreign Bodies in the Gastro-Intestinal Tract, Am. J. Surg. **72**:545-549, 1946.

105. Kenamore, B.: Removal of Foreign Bodies from the Stomach with a Permanent Magnet, Gastroenterology **8**:90-91, 1947.

106. Silber, S., and Epstein, B. S.: The Peroral Removal of Certain Swallowed Foreign Bodies Without Endoscopy, New York State J. Med. **47**:1122-1124, 1947.

107. Brown, C. H.; Colvert, J. R., and Brush, B. E.: Gastro-Ileostomy: A Rare Surgical Error; Symptoms and X-Ray Findings, Gastroenterology **8**:71-81, 1947.

nation was helpful in diagnosis. In 2 of the 3 cases refilling of the stomach was observed after it had emptied. In 1 case the short loop of the ileum that passed directly from the stomach to the colon could be seen filled with barium. In 2 of the cases the condition responded promptly to simple disconnecting of the "gastroenterostomy." The third patient at operation was found to have a gastroileostomy opening within several inches of the ileocecal valve. Two marginal ulcers were present.

Gastrocolic Fistula.—Roentgen studies were carried out on 7 dogs with experimentally induced gastrocolic or enterocolic fistulas and on 10 patients with gastrocolic fistula.[108] All or the major portion of the aliment passed from the stomach into the upper intestine, and practically none was shunted through the fistula into the colon. Two to six months after the experimental operative procedure a syndrome developed in the dogs consisting of a microcytic hypochromic anemia, intermittent diarrhea, steatorrhea, loss of weight and malnutrition. Gastric inflammation was present in 5 and ulceration in 2 animals. A subacute to chronic inflammatory infiltration, limited almost exclusively to the mucosa of the papillae, was present in the upper third of the small intestine. There was a tendency for the microcytic anemia to become macrocytic and hyperchromic in those animals surviving for a sufficiently long time. In a later report[109] the clinical manifestations are attributed to impairment of the digestive and absorptive functions of the small intestines as a result of the passage of colonic contents through it.

Ectopic Smooth Muscle.—Lattes[110] found conspicuous bundles of smooth muscle in the mucosa of the antral region in 56 of 100 unselected stomachs surgically removed for various reasons.

Tuberculosis.—Tuberculosis of the stomach was diagnosed for a 35 year old woman with a persistent prepyloric roentgen defect, gastric retention and anacidity.[111] The diagnosis was confirmed by histologic examination of a lymph node removed from the lesser curvature of the stomach at operation. Two years later tuberculous ulcerative colitis developed and a granuloma of the rectum, which was removed and contained acid-fast bacilli. Roentgenograms of the lungs showed no evidence of pulmonary involvement.

Gastric Arteriosclerosis.—Episodes of severe intermittent gastric bleeding over a period of thirty years in a 44 year old man were found at autopsy to be caused by advanced arteriosclerosis of extraordinarily

108. Renshaw, R. J. F.; Templeton, F. E., and Kiskadden, R. M.: Gastrocolic Fistula: A Clinical and Experimental Study, Gastroenterology **7**:511-521, 1946.

109. Kiskaddon, R. M.; Templeton, F. E., and Renshaw, R. J.: Gastro-Colic Fistula: A New Concept of Pathologic Physiology; Mechanism of Production of the Syndrome, Cleveland Clin. Quart. **14**:94-107, 1947.

110. Lattes, R. Ectopic Smooth Muscle in the Human Gastric Mucosa, Am. J. Path. **23**:501-505, 1947.

111. Windwer, C.: Tuberculosis of the Stomach, Rev. Gastroenterol. **13**:38-41, 1946.

large submucosal branches of the gastric arteries. Recurrent pulmonary tuberculosis was the cause of death.[112]

Hereditary Hemorrhagic Telangiectasia.—Kushlan [113] discusses the rare entity of hereditary hemorrhagic telangiectasia and presents observations made in 1 case, including gastroscopic findings. A favorable response to therapy with rutin apparently was obtained.

Polyps and Miscellaneous Tumors.—Ten gastric polyps and three additional possible polyps were found in 1,725 gastroscopic examinations.[114] The clinical features were not diagnostic. It is recommended that small asymptomatic polyps, appearing benign at gastroscopy, not be removed. Surgical intervention is indicated when there is a suggestion of malignancy, when the polyps are large or when complications such as obstruction occur. Similar views are expressed by Rappeport.[115] Interesting reports are presented of single polyps containing aberrant pancreatic tissue,[116] fibroma,[117] adenoma of the stomach,[118] gastric lipoma,[119] ganglioneuroma,[120] plasmacytoma producing complete pyloric obstruction[121] and an argentaffinoma causing gastroduodenal invagination. [122]

GASTRIC CANCER

Survey of the Problem.—In a comprehensive review of the problem

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112. Frank, W.: Hematemesis Associated with Gastric Arteriosclerosis, Gastroenterology **7**:231-240, 1946.

113. Kushlan, S. D.: Gastro-Intestinal Bleeding in Hereditary Hemorrhagic Telangiectasia, Gastroenterology **7**:199-212, 1946.

114. Paul, W. D., and Logan, W. P.: Polyps of the Stomach with Reference to the Gastroscopic Findings, Gastroenterology **8**:592-606, 1947.

115. Rappeport, J. H.: Gastric Polyposis, New Orleans M. & S. J. **99**:71-78, 1946.

116. Collett, R. W.: Prepyloric Polyp in Stomach of Child Diagnosed Histologically as Aberrant Pancreatic Tissue, Am. J. Dis. Child. **72**:545-551 (Nov.) 1946. Barbosa, J. de C., and Waugh, J. M.: Heterotopic Pancreatic Tissue, Clinically Significant, in the Gastric Wall of a Boy Six Years of Age, Proc. Staff Meet., Mayo Clin. **22**:25-30, 1947.

117. Rusker, W. H.: Fibroma of the Stomach, Minnesota Med. **29**:1042-1044, 1946.

118. Brocher, J. E. W., and Queloz, M.: Sur un adenome de la petite courbure, Gastroenterologia **71**:321-326, 1946. Colillas, D.; Bazterrica, E., and Garay, C. A.: Adenoma del estomago, Bol. y trab. Acad. argent. de cir. **30**:387-398, 1946. Bonamy, M., and Rubens-Duval, A.: Adenomatose diffuse de la muqueuse gastrique, Arch. d. mal. de l'app. digestif **35**:303-307, 1946.

119. Morichau-Beauchant, J.; Debelut, J., and Payard, J. M.: Image radiologique d'une tumeur intragastrique, Arch. d. mal. de l'app. digestif **35**: 52-54, 1946.

120. Pitts, H. H., and Hill, J. E.: Case Reports: Ganglioneuroma of Stomach, Canad. M. A. J. **56**:537-539, 1947.

121. Schwander, H.; Estes, J., and Cooper, W. G.: Plasmacytoma of the Stomach, Am. J. Path. **23**:237-242, 1947.

122. Jungmann, H.: Gastro-Duodenal Invagination, Brit. J. Radiol. **19**:292-296, 1946.

of gastric cancer, Barrett [123] points out that present statistics dealing with various experimental and clinical aspects are not entirely adequate. Further studies should be directed toward the role of genetic factors and the relationship of gastric cancer to pernicious anemia, achlorhydria and atrophic gastritis, diet and sex hormones. Proof of the exact relationship of gastric cancer to gastric ulcer is lacking, and additional experimental evidence on this problem is needed. New or improved methods for the diagnosis of early gastric cancer are urgently required. Investigation of the relation of mucus and bile to gastric cancer is desirable. The establishment of a gastric cancer registry might lead to more fruitful attacks on the problem. Ivy [124] subscribes to these views and in addition indicates the need for further education of the medical profession, surveys to find areas of high incidence and a more effective detection program.

Experimental Observations.—The repeated direct alimentary administration of hot water, hydrochloric acid, sodium hydroxide, lactic acid or atropine sulfate, with or without an emulsion of 1, 2, 5, 6-dibenzanthracene, failed to produce cancer or precancerous lesions in the gastric mucosa of mice of strains A, I and CsH and in hybrid LA mice (strain L crossed with mice of strain A).[125] Repeated parenteral injections of methyl chloride or of atropine sulfate, with and without direct alimentary administration of 1, 2, 5, 6-dibenzathracene, were likewise ineffective in producing any specific pathologic changes in the gastric mucosa of mice. That the stomach showed so little injury after drastic treatment is evidence of the remarkable resistance and recuperative power of the mucosa.

Strong [126] presents additional data regarding the development of cancerous lesions in the gastric mucosa of 540 mice following the subcutaneous injection of methycholanthrene. The lesions have occurred in mice from the F5 to F18 generations inclusive. The author concludes that a hereditary disease or a hereditary susceptibility to a disease, gastric cancer in mice, has been induced with chemical means. A multiplicity of pathologic lesions arising just anterior to the pylorus are probably biologically related, all being derived from the same or from similar embryologic defects and very likely the resultant of a biologic variability brought about by (1) the process of hybridization and (2) the induction of germinal mutations by methylcholanthrene or one of its metabolites.

123. Barrett, M. K.: Avenues of Approach to the Gastric Cancer Problem, J. Nat. Cancer Inst. **7**:127-157, 1946.

124. Ivy, A. C., in Discussion of a Comprehensive Outline of Attack on Gastric Cancer, J. Nat. Cancer Inst. **7**:404-407, 1947.

125. Dyer, H. M.; Kelly, M. E., and Dunn, T. B.: Effect of Administration of Hot Water, Acids, Alkali, Metholyl Chloride or Atropine Sulfate upon the Gastric Mucosa of Mice, J. Nat. Cancer Inst. **7**:67-71, 1946.

126. Strong, L. C.: Further Observations on the Genetic Nature of Gastric Cancer in Mice, J. Nat. Cancer Inst. **7**:305-308, 1947.

McPeak and Warren [127] describe in detail the gross and microscopic characteristics of the lesions and conclude that a definitive classification is not possible at the present time. The reviewers have failed to find evidence that the lesions described by Strong are in fact adenocarcinomas. Strong is a geneticist rather than a pathologist; the pathologists seem unconvinced. Consequently, final judgment with regard to this apparently important work must be deferred until conclusive pathologic proof is presented.

In experiments by Lushbaugh [128] 7 monkeys were exposed to a shale oil; 6 died during or shortly after the one hundred day exposure period. Hyperplastic gastritis, polyps and penetration of the submucosa by epithelial growths were found in the 2 monkeys surviving the longest; the seventh monkey, alive one and a half years later, was killed and found to have severe atrophic gastritis. The relationship of these types of gastritis to neoplasia remains to be determined; however, the preliminary observations suggest an interesting approach to this important problem.

The daily oral administration of 15 mg. of 20-methylcholanthrene to rabbits in which a "chronic" gastric ulcer had been produced surgically did not result in any detectable change in the ulcer in the domestic rabbits after periods of 3.5 to 5.5 months.[129] In similarly treated wild rabbits formation of epithelial cysts occurred in 3 of the 4 animals subjected to autopsy after five to thirteen months.

In a series of thirty-five experiments quinine was given either by mouth or by vein from two to six hours preoperatively to a group of patients with carcinoma of the tongue, esophagus, stomach or colon, and the tissues were studied for their quinine content.[130] The results suggest that quinine is selectively concentrated by neoplastic tissue, although the extent of the concentration is too small to be of any immediate significance.

The human stomach concentrates radioactive iodine to a considerable degree after the intravenous administration of 4 microcuries of radioiodine and 0.01 mm. of sodium iodide per kilogram of body weight.[131] The salivary glands excrete the radioiodine usually in higher concentration than the stomach. No definite conclusions can be drawn as yet con-

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127. McPeak, E., and Warren, S.: The Pathology of Gastric Carcinoma in Mice, J. Nat. Cancer Inst. **7**:309-311, 1947.

128. Lushbaugh, C. C.: Experimental Hyperplastic Gastritis and Gastric Polyposis in Monkeys, J. Nat. Cancer Inst. **7**:313-320, 1947.

129. Ivy, A. C., and Cooke, A.: An Attempt to Produce Malignant Transformation of Gastric Ulcer in Rabbits: A Preliminary Report, J. Nat. Cancer Inst. **7**:345-348, 1947.

130. Kelsey, F. E., and Brunschwig, A.: Concentration of Quinine in Gastrointestinal Cancers: Preliminary Report, J. Nat. Cancer Inst. **7**:355-356, 1947.

131. Schiff, L.; Stevens, C. D.; Mahl, W. E.; Steinberg, H.; Kumpe, C. W., and Stewart, P.: Gastric (and Salivary) Excretion of Radioiodine in Man: Preliminary Report, J. Nat. Cancer Inst. **7**:349-354, 1947.

cerning the influence of gastric disease, such as cancer, other tumors and peptic ulcer on the ability of the stomach to concentrate radioiodine.

Pernicious Anemia and Gastric Cancer.—In serial roentgenologic and gastroscopic examination of 211 patients with pernicious anemia, described by Rigler and his associates two years ago, 17 (8.0 per cent) were found to have carcinoma and 15 (7.1 per cent) benign polyps. Since then 48 new patients with pernicious anemia have been examined, with demonstration of one additional cancer and two benign polyps. These data provide further evidence that carcinoma of the stomach is more prevalent among persons with pernicious anemia than among the general population. The nature of this relationship remains obscure, but the evidence suggests that the two diseases are related etiologically.[132]

Benedict [133] points out that gastric atrophy is a definite disease possibly caused in part by an inflammatory process and in part by a state of deficiency. Gastroscopically, there is evidence that in some cases the gastric mucosa improves after prolonged, intensive liver therapy; pathologic proof of such improvement thus far has not been obtained. The high incidence of neoplasm in patients with gastric atrophy is again borne out.

Gastric Secretion.—In an attempt by State, Varco and Wangensteen [134] to identify the precursors of gastric cancer, gastric analyses were performed for 1,253 patients over the age of 50; achlorhydria to three successive 0.5 mg. doses of histamine was found in 238 and to one dose only in an additional 45. An additional 20 patients were found to have less than 20 clinical units of free acid. In these groups there were three carcinomas of the stomach and ten polyps. In a group of 84 achlorhydric persons observed in a previous study five additional polyps were found. No carcinoma was encountered in 79 patients with pernicious anemia examined roentgenologically. Forty relatives of 20 patients with gastric carcinoma were examined, but no cancer was found. Of 40 patients with occult blood in the stool, 34 were submitted to roentgenologic study; no unsuspected cancer was found. Of 20 patients with hemoglobin values below 11.0 Gm., roentgenograms of the stomach were made on 10; none of these had carcinoma.

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132. Kaplan, H. S., and Rigler, L. G.: Pernicious Anemia and Susceptibility to Gastric Neoplasms, J. Lab. & Clin. Med. **32**:644-653, 1947. Rigler, L. G., and Kaplan, H. S.: Pernicious Anemia and Tumors of the Stomach, J. Nat. Cancer Inst. **7**:327-332, 1947.

133. Benedict, E. B.: Observations on Gastric Atrophy After Liver Therapy, J. Nat. Cancer Inst. **7**:321-325, 1947.

134. State, D.; Varco, R. L., and Wangensteen, O. H.: An Attempt to Identify Likely Precursors of Gastric Cancer, J. Nat. Cancer Inst. **7**:379-385, 1947.

An important study by Comfort, Kelsey and Berkson [135] disclosed that achlorhydria was present in 127 (45.8 per cent) of a series of 277 cases of gastric cancer in which gastric analysis (modified Ewald test) was performed two or more years before the cancer was diagnosed. In the 150 cases in which the gastric contents contained acid the mean free acid was 35.3 clinical units at an average of 11.2 years before the diagnosis of cancer was made. A subnormal gastric secretory activity was characteristic of these patients with precancerous lesions regardless of the decade of life in which the initial test meal was given and also at all intervals in the years before cancer was diagnosed, even being present for as long as twenty to twenty-five years and more before the cancer developed. The mean secretory activity of the 186 patients for whom gastric analysis was carried out at the time of the diagnosis of cancer as well as at the initial investigation decreased in the interval between the two analyses. The percentage of patients who had achlorhydria increased to 68.8, and the mean acidity value among those with acid diminished to 31.6 clinical units. The process responsible for the lowering of gastric acidity appears to have been progressive but selective, because the gastric acidity did not appreciably decrease in all cases.

Cytologic Elements of Gastric Fluid.—Examination of the cellular elements of gastric fluid obtained by aspiration of the fasting stomach was carried out by a technic first applied in the diagnosis of cancer of the female genital tract.[136] Among the 27 cases of cancer a false negative diagnosis was made in 10, a diagnosis of suspected cancer in 7 and a positive diagnosis in 10. Three of the 10 patients for whom cancer was not diagnosed were found to have scirrhous lesions; in 3 others the cells were poorly preserved. In the 110 cases without gastric cancer a false positive diagnosis was made in none and a diagnosis of suspected cancer in only 9.

Metabolic Disturbances.—Patients with gastric cancer have faulty hepatic glycogen formation, which can be corrected by the administration of an adrenal extract, according to Rhoads.[137] Application of the Kepler test for Addison's disease has yielded results in patients with gastric cancer which resemble more closely those seen in Addison's disease than those present in any other disorder of known origin. In addition, there is a high incidence of hypoproteinemia, with an impaired capacity for regeneration of plasma proteins.

Diagnosis.—Problems in the diagnosis of gastric carcinoma are re-

135. Comfort, M. W.; Kelsey, M. P., and Berkson, J.: Gastric Acidity Before and After the Development of Carcinoma of the Stomach, J. Nat. Cancer Inst. 7:367-373. 1947.

136. Papanicolaou, G. N., and Cooper, W. A.: The Cytology of Gastric Fluid in the Diagnosis of Carcinoma of the Stomach, J. Nat. Cancer Inst. 7:358-359, 1947.

137. Rhoads, C. P.: Studies of Patients with Gastric Cancer, J. Nat. Cancer Inst. 7:333-336, 1947.

viewed by Golob.[138] Anglem [139] emphasizes the difficulty of early diagnosis. The average interval from the onset of symptoms to the first visit to a physician was nine months; the interval from the onset of symptoms to the establishment of diagnosis averaged seventeen months. It is to be noted that in 24 per cent of the cases the first roentgenogram failed to establish the diagnosis. Hudson and Alt,[140] on the basis of 60 cases studied between 1917 and 1945, found only slight improvement in diagnosis and in the surgical results.

In a study by Maimon and Palmer [141] the symptoms at the time of diagnosis were found to be of less than three months' duration in one fourth of the cases and of less than six months' duration in 53.7 per cent. Gastroscopy yielded the correct diagnosis in 84.6 per cent of the cases in which it was utilized. Roentgen examination provided the correct diagnosis in 91.8 per cent of the patients so examined. Attention is again directed to the need for prompt roentgenologic and gastroscopic study of patients with "dyspeptic" symptoms. In contrast to the preceding report, a trend toward earlier diagnosis is detected. Katsnelson [142] states that in Russia approximately 70,000 people die each year of cancer of the stomach. Present methods of diagnosis are reviewed, and the author reiterates the need for the thorough examination of all patients who have reached the so-called cancer age.

The importance of a competent roentgen examination of the stomach for all persons with digestive complaints, regardless of how mild they may appear, and for all those with predisposing diseases, such as pernicious anemia, in the early diagnosis of gastric cancer is emphasized by Crismer,[143] Dailey,[144] Templeton [145] and Giles.[146] A plan is presented

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138. Golob, M.: Gastric Carcinoma: Review of Errors in Diagnosis, Am. J. Digest. Dis. **13**:17-23, 1946.

139. Anglem, T. V.: Dyspepsia, Ulcer and Gastric Cancer, New England J. Med. **235**:322-325, 1946.

140. Hudson, P. B., and Alt, R.: Carcinoma of the Stomach, Am. J. Surg. **72**:202-211, 1946.

141. Maimon, S. N., and Palmer, W. L.: Gastric Carcinoma: Incidence and Diagnostic Procedures, Surg., Gynec. & Obst. **83**:572-574, 1946.

142. Katsnelson, S. M.: Recognition of Gastric Carcinoma, Am. Rev. Soviet Med. **4**:134-141, 1946.

143. Crismer, R.: Contribution a l'étude du diagnostic radioclinique précose du cancer gastrique: Examen général de la question et presentation de deux cas personnels, Rev. med. Liége **2**:11-20, 1947.

144. Dailey, M. E.: The Role of Cancer-Prevention Clinics in the Detection of Early Gastric Cancer, J. Nat. Cancer Inst. **7**:375-377, 1947.

145. Templeton, F. E.: Gastric Carcinoma: Can an Increased Diagnostic Accuracy Greatly Improve Survival Rates?, J. Nat. Cancer Inst. **7**:385-386, 1947.

146. Giles, R. G.: Roentgenological Consideration of Gastro-Intestinal Disturbances with Special Reference to the Stomach and Duodenum, South. M. J. **39**:570-574, 1946.

for the utilization of mass fluoroscopic and roentgenologic studies as a means of discovering curable lesions.[147]

Gastroscopy and Gastric Cancer.—Moersch and Kirklin [148] reviewed 100 selected cases of carcinoma of the stomach in which the diagnosis proved difficult, for the purpose of evaluating the accuracy of the gastroscopic and roentgen examination. In 10 instances it was impossible to make a definite diagnosis gastroscopically because of inadequate visualization; the roentgenologist experienced difficulty in arriving at a definite diagnosis in 6 cases. The gastroscopist's interpretation proved to be wrong in 20 cases, whereas the roentgenologist's opinion was incorrect in 42 cases. The source of greatest error in gastroscopic diagnosis was in the differentiation of carcinoma from severe hypertrophic gastritis; the error from this source was made eleven times. The roentgenologist experienced the same difficulty in 10 instances, misinterpreting the carcinomatous process as gastritis. Five ulcers regarded as benign gastroscopically proved on histopathololgic examination to be malignant; a similar error was made by the roentgenologist in 14 instances. Moersch and Kirklin conclude that histopathologic examination of the lesion remains the most accurate method of distinguishing between benign and malignant ulcer. However, the close collaboration of the gastroenterologist, roentgenologist and gastroscopist improves the likelihood of early correct diagnosis. In a later report, Moersch [149] concludes that gastroscopy is of value in the differential diagnosis between carcinoma and gastritis. It is not infallible, however, there being an incidence of error of approximately 10 per cent. Palpation of the stomach during gastroscopy may induce peristalsis and bring into view areas otherwise not visualized. Schlindler [150] found that gastroscopy and roentgen examination each yielded the correct diagnosis in 92.3 per cent and the incorrect diagnosis in 7.7 per cent.

Coexistent Ulcer and Cancer.—Three cases of coexistent benign ulcer and carcinoma are described by Yarnis.[151] The rarity of concurrent duodenal ulcer and gastric carcinoma is emphasized in a report by Fischer.

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147. Abrahamson, R. H., and Hinton, J. W.: Gastric Carcinoma: A Comparative Review of the Origin, Diagnosis and End-Results in Five Hundred and Eighty-Three Patients, Surg., Gynec. & Obst. **84**:481-490, 1947.

148. Moersch, H. J., and Kirklin, B. R.: Gastroscopy and Its Relationship to Roentgenology in the Diagnosis of Carcinoma of the Stomach, Gastroenterology **7**:285-293, 1946.

149. Moersch, H. J.: The Gastroscopic Differentiation of Gastritis from Carcinoma of the Stomach, Gastroenterology **8**:284-292, 1947.

150. Schindler, R.: What Does Gastroscopy Offer in the Early Diagnosis of Cancer of the Stomach?, California Med. **66**:110-116, 1947.

151. Yarnis, H.: Coexisting Ulcer and Cancer of the Stomach, S. Clin. North America **27**:299-307, 1947.

Clagett and McDonald,[152] who found only 48 proved cases in a series of 13,000 cases of carcinomas of the stomach. The age and sex incidence were approximately the same as in carcinoma of the stomach in general. The survival rate in this group of cases was considerably higher than that usually found in carcinoma.

"Carcinomatous Transformation."—On the basis of a pathologic study of surgically resected specimens, Koszewski [153] concludes that the incidence of carcinomatous transformation from ulcer is 14.63 per cent, as compared with an incidence of 3.0 per cent in necropsy studies. The author considers the real incidence to be between these two figures. The reviewers disagree with these figures and conclusions because there is no pathognomonic sign to indicate that a given ulcerating carcinoma began as a benign ulcer and underwent "malignant degeneration or transformation." Peptic activity may produce in a neoplasm the architecture of a benign ulcer and all the alleged criteria of preexisting benign ulcer.

Unusual Clinical Features.—Carcinoma in a boy aged 15, treated by subtotal gastrectomy of the Polya type, was found to be an ulcerated epithelioma with multiple metastases to lymph nodes.[154] The boy was alive six months after operation. An analysis of cancer of the stomach in 92 children and adolescents indicated that the condition is extremely rare in persons under 20 years of age but ceases to be exceptional in persons over this age. Epithelioma was present in 69 of the 92 patients, sarcoma in 17 and Krukenberg's tumor in 6. The symptomatology in children did not differ from that in the adult.

Three adenocarcinomas of the stomach invading the gastric wall simulated roentgenologically an extramucosal tumor.[155]

Boyce [156] reports a series of 36 perforating neoplasms, an incidence of approximately 2 per cent. Thirty-one of the patients were males and 5 females.

Acanthosis nigricans in a patient with an ulcerating cancer of the gastric antrum apparently regressed after removal of the neoplasm.[157]

Surgical Treatment and Results.—The numerous statistical analyses of the results of surgical treatment for gastric cancer are rather con-

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152. Fischer, A.; Clagett, O. T., and McDonald, J. R.: Coexistent Duodenal Ulcer and Gastric Malignancy, Surgery **21**:168-174, 1947.

153. Koszewski, von B. J.: Zur Frage der Häufigkeit des Ulkuskarzinoms des Magens, Gastroenterologia **71**:210-232, 1946.

154. Funck-Brentano, and Tubiana, R.: Cancer of Stomach in First Two Decades of Life, Semaine d hôp. Paris **23**:1171-1173, 1947.

155. Lowman, R. M.; Shapiro, R. and Kushlan, S. D.: Extramucosal Tumors Simulated by Gastric Carcinoma, Am. J. Roentgenol. **57**:726-735, 1947.

156. Boyce, F. F.: Perforated Gastric Malignancy, Surg., Gynec. & Obst. **83**:718-724, 1946.

157. Warmoes, F., and Goubau, P.: Un cas d'acanthosis nigricans en relation avec un cancer a l'estomac, Acta gastroenterol. belg. **9**:219-222, 1946.

fusing, for there are different ways of approaching the problem; varying standards are used, and particular aspects of the subject are emphasized. To the reviewers there seems to be a slight trend toward earlier operation, a definite trend toward a higher resectability rate, a lower mortality rate and longer postoperative survivals in a higher percentage of the patients.

Schindler,[158] in a series of 107 patients with resected carcinomas, found that only 7 survived for three years. In 6 of these the tumors were sharply localized, and of types I and II in the Borrmann classification; one was an infiltrative lesion. After five years only 4 patients were known to be alive.

Laparotomy performed in 83.5 per cent of 466 patients at the University of Chicago[159] resulted in a resectability rate of 43.5 per cent, with a survival rate of 32.2 per cent. Among 203 patients who underwent resection the survival rate was 73.7 per cent. The mortality for gastric resection of all types was 26.1 per cent for the seventeen years. Peritonitis was the chief cause of postoperative death. No residual carcinoma was demonstrated at autopsy in 25 per cent of the patients who died from gastric resection.

Harnett[160] reviews observations on 1,405 patients with cancer of the stomach treated in London hospitals during 1938 and 1939. The operability rate was 49.2 per cent and the resectability rate 17.3 per cent. The operative mortality for all radical operations averaged 32.9 per cent, ranging from 25.4 per cent for the Polya method of partial gastrectomy to 90 per cent for total gastrectomy. The survival rate for all radical operations averaged 23.1 per cent in traced cases after operative fatalities were excluded. Resection before the lymph nodes were involved resulted in a 60 to 63 per cent normal expectation of life over a five year period. After involvement of the lymph nodes, resection resulted in only a 40 to 43 per cent normal life expectancy. The average for all patients, including those not treated, was 27.4 per cent of normal. Women had the best survival rate.

In a series of 419 patients the lesion was found inoperable in 48.2 per cent.[161] Exploratory laparotomy and biopsy were done in 19.4 per cent, a palliative operation in 8.3 per cent and a partial gastrectomy in 24.1

158. Schindler, R.: Relative Surgical Curability of Certain Gross Types of Gastric Carcinoma, Surg., Gynec. & Obst. **83**:453-461, 1946.

159. Maimon, S. N., and Palmer, W. L.: Gastric Cancer: Laparotomy, Resectability, and Mortality, Surg., Gynec. & Obst. **83**:480-484, 1946.

160. Harnett, W. L.: Statistical Study of 1405 Cases of Cancer of the Stomach, Brit. J. Surg. **34**:379-385, 1947.

161. Marshall, S. F., and Welch, M. L.: Carcinoma of the Stomach: Rate of Operability, S. Clin. North America **27**:631-635, 1947.

per cent. Eliason and Witmer [162] review 149 cases observed from 1929 to 1934; 64 per cent of the patients were males, with 81 per cent between the ages of 40 and 70. The surgeon was consulted three months or longer after the onset of symptoms in 75 per cent of the cases and one year or more in 42 per cent. In only 52 cases was the condition operable; there were three five year cures.

Pack [163] points out that improvement in end results may be attributed to a greater awareness on the part of the general public, improved facilities for the diagnosis of cancer, a wider application of surgical resection by an increased number of surgeons and, finally, the introduction of extremely radical surgical procedures of three types, namely, removal of the organs adjacent to the stomach involved by contiguity, total gastrectomy when the cancer involves the major part of the stomach and transthoracic, transdiaphragmatic cardiectomy for cancers involving the cardia. Better appreciation of proper preoperative and postoperative care of the patient are important additional factors.

Improved results are indicated in a series of papers dealing with total gastrectomy. Marshall and Brown [164] report a surgical mortality of 43.4 per cent during the period 1929 to 1942 and of 16.3 per cent from 1942 to January 1947. Eighty-nine patients, 88 with neoplasm, underwent a complete gastrectomy,[165] with a mortality of 29.1 per cent. The mortality during the last three years and nine months of the study was 16.3 per cent. Twelve patients have survived the operation for three or more years. Of 20 patients subjected to total gastrectomy by Longmire,[166] 2 died; 7 patients survived more than a year and resumed their previous occupations. In a series of 98 radical resections for gastric cancer Ischchenko [167] found a mortality of 13.2 per cent. Wahren [168] performed 9 total resections, and there were no deaths. Buschmann [169] reports an advanced adenocarcinoma with local metastasis successfully treated by combined gastrectomy and colectomy.

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162. Eliason, E., and Witmer, R. H.: Surgical Aspects of Carcinoma of the Stomach, Am. J. Surg. **72**:679-682, 1946.

163. Pack, G. T.: The Radical Surgical Treatment of Gastric Cancer, J. Nat. Cancer Inst. **7**:337-344, 1947.

164. Marshall, S. F., and Brown, L. H.: Total Gastrectomy, S. Clin. North America **27**:621-635, 1947.

165. Smith, F. H.: Total Gastrectomy: Report of Eighty-nine Cases, Surg., Gynec. & Obst. **84**:42-408, 1947.

166. Longmire, W. P.: Total Gastrectomy for Carcinoma of the Stomach, Surg., Gynec. & Obst. **84**:21-30, 1947.

167. Ischchenko, I. N.: Gastric Resection for Cancer, Am. Rev. Soviet Med. **4**:130-134, 1946.

168. Wahren, H.: Total Resection of the Carcinomatous Stomach, Acta chir. Scandinav. **95**:193-204, 1947.

169. Buschmann, T. W.: Advanced Carcinoma of Stomach Requiring Combined Gastrectomy and Colectomy, Northwest Med. **46**:126-127, 1947.

Neibling and Walters [170] report a total gastrectomy with esophagoduodenal anastomosis for diffuse linitis plastica of the stomach in a 65 year old woman. Apart from a minimal phlebitis on the seventeenth day, the postoperative course was uneventful and the patient made a good recovery. Prior to 1945, three such operations were performed at the Mayo Clinic. The first 2 pateints died while still in the hospital. The third patient and 3 others operated on since 1945, included the one just mentioned, have survived.

Allison [171] describes a technic for palliative esophagojejunostomy in the management of irremovable carcinoma of the cardia.

PEPTIC ULCER

Experimental Observations.—According to LeVeen,[172] the effect of acids is to enhance the activity of pepsin rather than to produce ulceration by itself. Irrigations of the terminal end of the ileum of the dog with hydrochloric acid at a p_H of 1.5 and a temperature of 40 C. produced a brownish discoloration of the mucosal surface due to precipitation of mucus, but no ulcers developed. Petechial hemorrhage, superficial ulceration and mucosal congestion occurred after irrigation with 1 per cent solution of pepsin at a p_H 1.5 and a temperature of 30 C. However, when pepsin activity was increased, a perforated ulcer 1.4 cm. in diameter developed. In general, ulcers formed more readily with solutions of increasing acidity. The secretion of mucus was stimulated by irrigations with acid solutions. Spasm of the bowel wall, by reducing the exposed surface area and increasing the secretion of mucus, apparently served as a protection from ulceration. Mucus presented a protective barrier, as evidenced by the fact that ulcers formed only in the area in which the stream of irrigation kept the mucosa free of mucus.

Various living tissues, including omentum, intestine, liver, gallbladder, pancreas, spleen, kidney, lung, cartilage, skin and the gastric wall itself, were implanted in the lumen of the stomach or maintained in prolonged surface contact with gastric secretion.[173] Virtually all the tissues and organs so tested underwent digestion; those most rapidly digested were the external coats of the intestines, appendix and gallbladder, and those most resistant were fibrous connective tissue, skin and intestinal mucosa. The one tissue which seemed to be resistant to ordinary digestion

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170. Neibling, H. A., and Walters, W.: Total Gastrectomy with Esophagoduodenal Anastomosis, Proc. Staff Meet., Mayo Clin. **21**:449-453, 1946.

171. Allison, P. R.: Oesophago-Jejunostomy for Irremovable Carcinoma of the Cardia, Thorax **1**:239-246, 1946.

172. LeVeen, H. H.: Chemical, Physiological, and Pathological Observations on the Role of Pepsin and Hydrochloric Acid in the Production of Experimental Ulcers, Gastroenterology **8**:648-661, 1947.

173. Price, P. B., and Lee, T. F.: The Gastric Digestion of Living Tissue, Surg., Gynec. & Obst. **83**:61-72, 1946.

was gastric epithelium. Tissues udergoing digestion manifested different types and degrees of reaction. Serous surfaces became acutely inflamed, with rapid leukocytic infiltration and necrosis. The capsules of liver, spleen and kidney responded with excessive amounts of fibrosis. Epidermal surfaces slowly eroded, with little or no cellular reaction. Active fibrosis and granulation tissue served to produce resistance to digestion. Once tissues were covered with proliferating gastric epithelium, they appeared to be safe from further corrosive action.

Twenty-four hours after ligation of the single artery and vein supplying the antrum, a single, penetrating 5 mm. ulcer developed in the center of the antrum in 10 of 18 rats.[174] Two perforations were observed. Unilateral ligation of the fundic vessels in 20 rats resulted in an intense purplish congestion of the mucosa; ulcer did not develop in 12 of the rats after twenty-four hours, but it did develop in 1 of 8 rats after forty-eight hours. Bilateral ligation of the fundic vessels produced mottled red to brown blotches in the mucosa. Twenty-four hours after ligation 5 of 8 animals had multiple ulcers in both halves of the fundus. Lack of anastomotic blood supply is postulated as the cause of these ulcers. Some rats were kept for eight to sixteen days after ligation, and all survived. Various stages of repair were observed; the fundic lesions showed more advanced healing, probably because of better collateral circulation.

Harris and others[175] induced ulcers in the forestomach of rats recovering from vitamin A deficiency and receiving 2, 30 and 300 units of vitamin A daily, rats recovering from vitamin B_6 deficiency and receiving suboptimal amounts of pyridoxine and rats recovering from a deficiency of essential fatty acids and receiving 20 mg. of linoleate daily. Ulcers occurred only in the recovery period. Tocopherol fed daily protected the rats against the formation of ulcers, whereas injected tocopherol phosphate did not.

Ulcers are provoked more readily in dogs and rabbits subjected to experimental burns when histamine is given.[176] Ulcers occurred in 2 of 11 animals subjected to burns alone (18.2 per cent), whereas in all the 14 dogs burned in addition to being exposed to histamine, erosion or ulcer was present. Friesen and Wangensteen[177] present evidence that gastro-

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174. Berg, B. N.: Gastric Ulcers Produced Experimentally by Vascular Ligation, Arch. Surg. **54**:58-66 (Jan.) 1947.

175. Harris, P. L.; Hove, E. L.; Mellott, M., and Hickman, K.: Dietary Production of Gastric Ulcers in Rats and Prevention by Tocopherol Administration, Proc. Soc. Exper. Biol. & Med. **64**:273-277, 1947.

176. Friesen, S. R., and Wangensteen, O. H.: Experimental Burns Accompanied by Histamine Administration Abets the Ulcer Diathesis, Proc. Soc. Exper. Biol. & Med. **63**:245-248, 1946.

177. Friesen, S. R., and Wangensteen, O. H.: Role of Hemoconcentration in Production of Gastric and Duodenal Ulcer Following Experimental Burns, Proc. Soc. Exper. Biol. & Med. **64**:81-85, 1947.

intestinal abnormality following burns, even when accompanied with administration of histamine, may be prevented by avoidance of hemoconcentration. Babkin and Lawson [178] successfully performed a gastroduodenoduodenostomy in a dog which remained in good health for more than a year. The fasting stomach always contained an average of 100 cc. of alkaline, bile-stained fluid; trypsin was present in high concentration. The absence of ulceration was attributed to the lowered acidity and peptic activity of the gastric contents.

Radiation.—Five patients with a variety of malignant lesions not involving the stomach received from 5,000 to more than 6,000 r, administered through two gastric portals, anterior and posterior, over a period of almost one month.[179] Diffuse inflammation of the stomach, erosions and ulceration were observed in all cases.

Betz [180] irradiated the abdominal wall of 29 rabbits with doses varying from 1,000 to 3,000 r and produced both diffuse and localized lesions in the mucosa. The diffuse lesions consisted of a direct alteration of the glandular elements in the following order of sensitivity: the superficial epithelium, the pyloric glands, the chief cells and the parietal cells. The localized lesions consisted of hemorrhages and ulcers. The small subepithelial hemorrhages disappeared rapidly; the localized hemorrhagic infiltration of the mucosa, found almost exclusively at the pyloric end or in the lesser curvature, was transformed into ulcers. The hemorrhagic necroses were secondary to lesions of the capillaries. The lesions were acute and were directly related to the amount of radiation administered. The animals receiving 2,400 r died after eight to ten hours, and the animals receiving 1,500 r died between the fifteenth and the twentieth hour. In 1 animal killed four hours after a dose of 3,000 r there was no macroscopic alteration. Three animals receiving 2,400 r had severe lesions; in 2 the lesions perforated. Of 2 animals receiving 1,800 r, 1 had no lesion after seven hours, and the other had superficial ulcers after nine hours. Of 20 animals given 1,500 r and killed within nine hours to nine days, 5 showed no lesion, 5 had hemorrhages and 10 had ulcers. In 1 animal receiving 1,200 r and in 2 receiving 1,000 r no abnormality was found.

Treatment of Experimental Ulcer.—Seven dogs were given 30 mg. of histamine in beeswax, intramuscularly, daily.[181] In 2 of the animals,

178. Babkin, B. P., and Lawson, R. N.: Gastroduodenoduodenostomy, Acta Med. Scandinav. (supp. 196) **128**:308-321, 1947.

179. Brick, I. B.: Radiation Effects on the Human Stomach, Rev. Gastroenterol. **13**:363-370, 1946.

180. Betz, H.: Contribution a l'étude de l'ulcère gastrique: I. Sur la production d'ulcères gastriques par irradiation abdominale chez le lapin, Rev. belge sc. méd. **17**:121-154, 1946.

181. Fast, J.; Friesen, S. R., and Wangensteen, O. H.: The Sippy Regimen Protects Against the Histamine-Provoked Ulcer, Gastroenterology **8**:662-664, 1947.

serving as controls, posterior duodenal ulcers were found after thirty-four and thirty-nine days. The five remaining dogs, subjected to gastrostomy, received a modified Sippy diet consisting mainly of milk and an alkaline mixture of 1.3 Gm. of sodium bicarbonate and 0.6 Gm. of bismuth subcarbonate alternately every hour from 8:00 a.m. to 7:00 p.m. The gastric contents were removed at 9:00 p.m. and 200 cc. of milk instilled. The diet was supplemented with horse meat, liver and vitamins after the first week. No ulceration or erosion was found in 4 dogs killed on the forty-first day.

"Benadryl hydrochloride" (N.N.R.) given to dogs with Pavlov or Heidenhain pouches by oral, subcutaneous and intravenous routes failed to alter the gastric secretory response to histamine and to protect against the histamine-provoked ulcer.[182] When given alone, it produced neither an increase nor a decrease in the level of gastric secretion in fasting dogs. The results indicate that "benadryl hydrochloride" is not a specific antagonist of histamine. Similar observations were made by Crane and others [183] on 16 adult albino guinea pigs given daily injections of 0.1 cc. of a histamine suspension in beeswax and oil (containing 100 mg. of histamine base per cubic centimeter) for eleven days. Eight of the animals were then given "benadryl hydrochloride" in quantities of 135 mg. per kilogram of body weight daily, administered in divided doses in sterile water intraperitoneally. Gastrc ulcers developed in 5 of the benadryl-treated animals, perforation occurring in 4. Six of the control group showed ulcers, of which four had perforated.

"Benadryl hydrochloride" given in doses sufficiently large to produce drowsiness had no influence on gastric motility or acidity in 6 patients.[184] Clinical improvement was observed in 5 of the group, but the authors correctly point out that peptic ulceration, with its characteristic remissions, is peculiarly unsuited for therapeutic trials assessed on a purely clinical basis.

Evaluation of various therapeutic agents used in the management of peptic ulcer was made to test their ability to protect the rumen of rats from ulceration after ligation of the pylorus.[185] Sodium dodecyl sulfate and colloidal aluminum hydroxide used in combination offered complete protection. When given singly, these preparations prevented ulcers in 80 per cent of the rats. Other agents in order of effectiveness were

182. Friesen, S. R.; Baronofsky, I. D., and Wangensteen, O. H.: Benadryl Fails to Protect Against the Histamine-Provoked Ulcer, Proc. Soc. Exper. Biol. & Med. **63**:23-25, 1946.

183. Crane, J. T.; Lindsay, S., and Dailey, M. E.: An Attempt to Prevent Histamine-Induced Ulcers in Guinea Pigs with Benadryl, Am. J. Digest. Dis. **14**:56-57, 1947.

184. Kay, A. W.; Scott, L. D. W., and Smith, W. E.: Observations on Use of Benadryl in Duodenal Ulcer, Glasgow M. J. **28**:145-148, 1947.

185. Shay, H.; Komarov, S. A.; Siplet, H., and Gruenstein, M.: An Evaluation of Some Antacid and Antipeptic Agents in the Prevention of Gastric Ulceration in the Rat, Am. J. Digest. Dis. **14**:99-103, 1947.

sodium aluminum trisilicate, magnesium oxide, dibasic aluminum aminoacetate, magnesium trisilicate and sodium bicarbonate.

After ligation of the pylorus, 480 ulcers were produced in 22 starved rats of a control series, whereas no ulcers developed in 20 vagotomized rats after ligation of the pylorus.[186] Ulcers occurring after pyloric ligation in rats were apparently prevented by the intravenous administration of 50 mg. of a neutral extract prepared from normal human urine.[187]

A method is described which utilizes a rat preparation for the assay of so-called anti-gastric-ulcer factors.[188] After a fasting period, lengthened with the age of the animal, the pylorus is ligated and fasting continued. Gastric juice accumulates in the stomach, and ulceration of the rumen ensues. In young rats extensive ulceration occurs in seven to nine hours, while in older rats a longer postoperative period is required. A proposed method of recording consists in a grading which ranges from "clear" for animals with no ulceration to 4 plus for those with the most extensive ulceration. Factors affecting the assay, such as technic of operation, age and sex of the animal and period of fast, are discussed. The gastric ulcers are attributed to peptic activity. Among 47 Sprague-Dawley albino male rats treated through various parenteral routes with enterogastrone in doses ranging from 20 to 500 mg. per kilogram for periods of one to thirty days rumenal ulcers developed in all but 1.[189] There was no correlation between the size of the dose, the length of treatment and the number of ulcers.

Mechanism of Ulcer Pain.—Bonney and Pickering [190] present highly significant data on the mechanism of pain in peptic ulcer. In 55 cases of gastric, duodenal or anastomotic ulcer and in a small number of cases of gastric cancer they found that ulcer pain was relieved by aspiration of the stomach and could be induced by reintroduction of the gastric contents; pain was not produced if the contents were neutralized prior to injection. Pain nearly always recurred when the gastric contents attained

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186. Harkins, H. N.: Prevention of Pyloric Ligation-Induced Ulcers of the Gastric Rumen of Rats by Trans-Abdominal Vagotomy: Preliminary Report, Bull. Johns Hopkins Hosp. **80**:174-176, 1946.

187. Wick, A. N.; Irish, A. J.; Pauls, F., and MacKay, E.: Preparation of an Anti-Ulcer Factor from Human Urine, Proc. Exper. Biol. & Med. **64**:40-44, 1947.

188. Pauls, F.; Wick, A. N., and MacKay, E. M.: An Assay Method for Anti-Ulcer Substances, Gastroenterology **8**:774-782, 1947.

189. Morris, C. R.; Grossman, M. I., and Ivy, A. C.: Failure of "Enterogastrone" to Prevent Rumenal Ulcers in the Shay Rat, Am. J. Physiol. **148**:382-386, 1947.

190. Bonney, G. L. W., and Pickering, G. W.: Observations on the Mechanism of Pain in Ulcer of the Stomach and Duodenum: I. The Nature of the Stimulus. Clin. Sc. **6**:65-89, 1946.

a certain degree of acidity for a sufficient time and was nearly always absent or subsiding when gastric acidity fell below a certain level for a sufficient time. In the pain-free periods and in normal subjects the introduction of acid did not induce pain. The threshold of acidity necessary to evoke pain varied greatly from one patient to another. In general, duodenal ulcer manifested the highest threshold and anastomotic ulcer the lowest, with gastric ulcer intermediate; in some cases of gastric carcinoma the threshold was still lower than that found in peptic ulcer. Thus, the p_H necessary to evoke pain was about 1.5 for patients with duodenal and gastric ulcer and as low as 2.75 in anastomotic ulcer. Intragastric pressure during pain induced by acid solutions usually was slightly lower than that observed in the absence of pain. Roentgenologic examination during pain revealed no localized contractions of the stomach or duodenum that were not present when pain was absent.

Bonney and Pickering also studied the time relations for the onset of pain when acid is applied to an experimentally produced ulcer of the skin.[191] The time required for the induction of pain by acid and for its relief by neutralization was found to be much shorter than that observed in cases of peptic ulcer. The time was slightly prolonged by covering the ulcer with a thin film of mucus. When, however, the skin ulcer was protected by a scab, the time relations were greatly prolonged and were then of the same order of magnitude as that observed in peptic ulcer. It seems, therefore, that the time relations of pain in the presence of peptic ulcer are related to the chemical stimulation of nerve endings situated in the ulcer crater and separated from the cavity of the stomach or duodenum by a layer of inert material. These findings confirm the previously reported observations of Palmer that pain in peptic ulcer results from the exposure of a defective mucus membrane to a sufficient concentration of hydrogen ions and that it is not due to general or local contraction of the stomach or duodenum.

General Observations.—Current concepts of gastroduodenal ulcer are reviewed by Eusterman.[192] Ivy,[193] in a stimulating discussion of the ulcer problem, points out that peptic ulcer develops in approximately 1,500,000 persons in the United States above the age of 30 during a period of ten years and that the disease will develop in 10 per cent of the population at some time in their lives. The predominance of duodenal ulcer and its greater incidence in males have not been explained. The postoperative

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191. Bonney, G. L. W., and Pickering, G. W.: Observations on the Mechanism of Pain in Ulcer of the Stomach and Duodenum: II. The Location of the Pain Nerve Endings, Clin. Sci. **6**:91-111, 1946.

192. Eusterman, G. B.: Newer Phases of Gastroduodenal Ulcer, Gastroenterology **8**:575-585, 1947.

193. Ivy, A. C.: The Problem of Peptic Ulcer, J.A.M.A. **132**:1053-1059. (Dec. 28) 1946.

gastrojejunal ulcer, caused chiefly by the action of acid on the jejunal mucosa, is the only ulcer occurring in man that has been reproduced experimentally. Ivy further states that adequate proof does not exist for the propositions that the patient with peptic ulcer has a characteristic personality pattern, that certain emotional states regularly induce gastric hyperactivity and that a state of gastric hyperactivity alone can cause peptic ulcer. The development of some therapeutically practical and innocuous method for increasing the resistance of the gastric, duodenal and jejunal mucosa to injury and for completely blocking the parietal cell is regarded as the most promising investigative approach to the ulcer problem.

Incidence.—Ulcer in South Australia is reviewed by Linn.[194] A marked increase in the incidence occurred in Belgium during the war years, with a particularly sharp increase in the frequency of gastric ulcer.[195] Knutsen and Selvaag[196] investigated the incidence of peptic ulcer during the year 1942 in a typical Norwegian town of 25,830 persons. Ulcer was found in 537 persons, or 2.08 per cent of the total population, and 2.45 per cent of the population above the age of 15. The ratio of men to women was 2.49 to 1. The ratio of gastric ulcer to duodenal ulcer was 1 to 1.85. Gastric ulcer was more frequent in the age groups above 50 and relatively more common among women than among men. There were 10 multiple ulcers of the stomach in a series of 200 roentgenologically demonstrated craters.[197]

Psychosomatic Relationships.—Crohn[198] reports several interesting cases in which recurrence of peptic ulcer and even perforation followed severe psychic trauma. Gainsborough and Slater[199] investigated a group of 130 men and 32 women with peptic ulcer psychiatrically and followed them after treatment for periods up to three years. The chief characteristics of the male patients were their energetic dispositions, tendency to anxiety, irritability, obsessionality and hypochondriasis. Their occupations and their school and work records revealed that the patients were good workers and somewhat superior to the average. Actual neurosis

194. Linn, H. W.: An Analysis of Peptic Ulcer in South Australia, Based on a Study of 1,027 Case Reports, M. J. Australia **2**:649-658, 1946.

195. DeWitt, J.: L'influence de la guerre mondiale sur la friquence et la localisation des ulcères gastroduodenaux, Acta gastro-enterol. belg. **9**:396-406, 1946.

196. Knutsen, B., and Selvaag, O.: The Incidence of Peptic Ulcer, Acta med. Scandinav. (suppy. 196) **128**:341-360, 1947.

197. DeBusscher, G.: A propos de quelques ulcères multiples de l'estomac en pleine période de guerre, Bruxelles med. **26**:939-943, 1946.

198. Crohn, B. B.: Peptic Ulcer as a Psychosomatic Disease, S. Clin. North America. **27**:309-314, 1947.

199. Gainsborough, H., and Slater, E: A Study of Peptic Ulcer, Brit. M. J. **2**:253-258, 1946.

was uncommon, but the rate was somewhat higher among the women than among the men. The stresses to which the patients were exposed prior to their illness were principally those inseparable from ordinary life today. Unusual psychologic situations and patterns were infrequent. Failure in healing of the ulcer was not encountered, but relapses occurred in about one third within four months after their return to work. Cathcart [200] emphasizes the dominant role of deep-seated emotional conflicts in the production of peptic ulcer, which is in accordance with the theory of Alexander that the patient with ulcer meets a strong tendency toward dependency by overstriving in the direction of independence and self sufficiency. Pegrallo [201] likewise is impressed with the role of psychic factors in the pathogenesis of peptic ulcer.

Moses [202] believes that a high alpha index of the electroencephalogram is associated with passive, dependent, receptive trends whereas a low alpha index is usually associated with a consistent, well directed, freely indulged drive to activity. A previous investigation of patients with ulcer revealed that 70 per cent manifested a dominant alpha index, as contrasted with a 20 per cent incidence in normal persons. In a further study of 25 patients with peptic ulcer, characterized by pronounced feelings of insecurity associated with strong passive dependent traits, 76 per cent were found to fall into the dominant alpha group.

On the other hand, in a study in an Army General Hospital in Hawaii Radloff [203] noted that ulcers rarely developed in psychoneurotic soldiers with gastrointestinal complaints and that they rarely gave a history compatible with the diagnosis of ulcer. Vomiting was infrequent in patients with ulcer and common in those diagnosed as psychoneurotic. Routine medical management produced complete symptomatic relief in seven to ten days. Massive hemorrhage responded well to transfusions and early feeding. No fatalities were recorded.

Steiner [204] found no disease of the stomach among Okinawans except ulcer; the lesions were acute and were thought to be related to the psychosomatic stress occasioned by the bombing and invasion of the island.

The reviewers admit that to them the role of emotional factors in the production of peptic ulcer and in its recurrence still is an enigma. They are inclined to accept the evidence that in many patients, at least, such

200. Cathcart, J. P. S.: The Role of the Emotions in the Production of Gastro-Intestinal Disturbances, Canad. M. A. J. **55**:465-470, 1946.

201. Peygrallo, R. A.: Componentes psiquicos de la úlcera gastro-duodenal, An. de cir. **11**:182-193, 1946.

202. Moses, L.: Psychodynamic and Electroencephalographic Factors in Duodenal Ulcer, Psychosom. Med. **8**:405-409, 1946.

203. Radloff, F. F.: Observations on Five Hundred and Forty-Three Cases of Peptic Ulcer, Gastroenterology **8**:343-347, 1947.

204. Steiner, P. E.: Necropsies on Okinawans: Anatomic and Pathologic Observations, Arch. Path. **42**:359-380 (Oct.) 1946.

factors are present and are sufficiently important to produce either an acute ulcer or a recurrence of a chronic lesion. It is also possible that entirely different mechanisms may be operative in other patients. Furthermore, the reviewers are skeptical of any specificity in the psychodynamic pattern.

Allergy.—Moutier [205] regards ulcer of the stomach as a disease of sensitization similar to other allergic syndromes such as eczema and urticaria but does not offer convincing evidence.

Gastric Secretion.—Caffeine-stimulated gastric secretion was measured in 20 patients with duodenal ulcer in remission, in 25 patients with active duodenal ulcer and in 10 normal persons.[206] The normal persons secreted an average total of 363 mg. of hydrochloric acid, the patients with ulcer in remission 361 mg. and the patients with active duodenal ulcer an average of 957 mg. The average concentration of hydrochloric acid in the normal persons was 86 mg. per hundred cubic centimeters; in patients with ulcer in remission it was 162 mg. and in patients with active duodenal ulcer 214 mg., or 149 per cent over that of the normal persons.

Sandweiss and his associates [207] studied the nocturnal secretion both in normal persons and in patients with uncomplicated duodenal ulcer; secretion was found to be continuous in both groups. When periodic aspirations were performed during the night, a greater volume was obtained from patients with duodenal ulcer than from normal persons. There was no statistically significant difference in the volume or in the total output of acid between the two groups when continuous aspirations were done. Studies made under the same conditions indicated that the curves of acid concentration vary considerably from one person to another, both normal and ulcer bearing, and also in the same persons on different nights. Sandweiss concludes that there is no difference between normal subjects and patients with uncomplicated duodenal ulcer as regards the volume and acidity of the gastric juice secreted during the night.

Other authors [208] have not been able to confirm the results of Sand-

205. Moutier, F.: Interprétation allergique de l'ulcère gastro-duodénal basée sur ses caractères cliniques (douleurs tardives) et anatomiques, Arch. d. mal. de l'app. digestif **35**:273-284, 1946.

206. Musick, V. H.; Avey, H. T.; Hopps, H. C., and Hellbaum, A. A.: Gastric Secretion in Duodenal Ulcer in Remission-Response to the Caffeine Test Meal, Gastroenterology **7**:332-339, 1946.

207. Sandweiss, D. J.: Friedman, M. D. F.; Sugarman, M.D., and Podolsky, H. M.: Nocturnal Gastric Secretion: II. Studies on Normal Subjects and Patients with Duodenal Ulcer, Gastroenterology **7**:38-54, 1946.

208. Levin, E; Hamann, A., and Palmer, W. L.: The Effect of Radiation Therapy on the Nocturnal Gastric Secretion in Patients with Duodenal Ulcer, Gastroenterology **8**:565-574, 1947.

weiss, whereas they have confirmed in essence those of Musick and others.[206]

The nocturnal gastric secretion was measured in 28 patients with duodenal ulcer.[208] The volume varied from 550 to 1,750 cc., with an average of 1,110 cc. The free acidity ranged from 18 to 122 clinical units, averaging 62. Nine of the patients were studied during the course of radiation therapy directed at the body and fundus of the stomach. Some reduction in the volume and in the free acidity was noted in 7; an increase was observed in 2 cases. Fifteen patients were studied at varying intervals after the completion of radiation therapy. Fourteen of these showed a decrease in volume, with an average reduction of 47 per cent. Thirteen patients exhibited complete anacidity in the nocturnal secretion; a considerable reduction in acidity occurred in the 2 remaining cases. A reduction in the secretory response to histamine stimulation was also noted in the 15 patients.

Ascorbic Acid.—Determinations of fasting plasma vitamin C levels and of the levels at one, two and three hours after a test dose of 1 Gm. of ascorbic acid in 13 patients with active peptic ulcer, in 7 with active hemorrhage, in 10 with asymptomatc ulcers under treatment and in 25 control patients disclosed that those with active ulcer manifested lowered initial levels, with flatter curves, after the test dose.[209] Patients with active ulcer and hemorrhage had the lowest levels. No appreciable diminution of the plasma vitamin C was found in the convalescing group. Statistical analysis of the data by the "t" test indicated significant differences between the control group and the patients having active and bleeding ulcers. It is concluded that vitamin C should be added to or included in the diets of patients with peptic ulcer.

Diagnostic Considerations.—Brown and Harper [210] recommend roentgen examination of the stomach and duodenum in the right lateral horizontal position as well as in the routine posteroanterior position for the diagnosis of duodenal ulcer.

Kay [211] reports rather unusual results in the diagnosis of active duodenal ulcer from testing, with a gastrogram, gastric motility in response to the ingestion of cold water. The test is based on the observation of Carlson (1916) that the ingestion of cold water inhibits gastric contractions for approximately five minutes and on that of Anderson (1943)

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209. Crescenzo, V. M., and Cayer, D.: Plasma Vitamin C levels in Patients with Peptic Ulcer: Response to Oral Load Test of Ascorbic Acid, Gastroenterology **8**:754-761, 1947.

210. Brown, S., and Harper, F. G.: Roentgen Diagnosis of Duodenal Ulcer in the Right Lateral Decubitus Position, Radiology **47**:575-582, 1946.

211. Kay, A. W.: Effect of Water on Gastric Motility: A Test for Duodenal Ulcer, Lancet **1**:448-450, 1947.

that patients with peptic ulcer either do not manifest this inhibition or show a reverse response (increased peristalsis). A tambour-kymograph unit, with a modification of Carlson's technic, was used. Thirty normal subjects manifested inhibition of gastric motility as expected. Sixty-eight of 90 patients with symptoms of duodenal ulcer and a roentgenologically demonstrable crater showed increased motility (reversed response), and 22 maintained their gastric contractions. A normal (inhibition) response was observed in 15 patients who had been symptom free for at least a year after perforation of a duodenal ulcer and whose roentgenograms did not demonstrate an active ulcer. A normal response was observed in 33 of 34 patients with gastric lesions (12 with ulcer and 22 with carcinoma). A reversed response was recorded in 1 patient with gastric carcinoma in whom invasion of the duodenum was revealed at laparotomy. Gastric contractions were excited in 2 of 9 patients with acute cholecystitis, and in 1 of these laparotomy revealed empyema of the gallbladder, which was adherent to the duodenum. Carlson's view that the inhibitory effect of cold water on gastric motility is due to afferent stimuli arising in the gastric mucosa should be modified, according to Kay, in favor of the theory that the receptors for their reflex are in the duodenum.

According to Gershon-Cohen,[212] the duodenum houses a mechanism influencing gastric tone, peristalsis, pyloric action and secretion. Experiments are cited to demonstrate that intraduodenal instillation of hydrochloric acid, hypertonic alkaline solution, other hypertonic solutions of electrolytes, fats or fatty acids inhibits gastric peristalsis and induces pyloric closure. A critical threshold level of stimulation of the "duodenal mechanism" regulates the peak of acid gastric secretion. Because this threshold level is altered by the inflammatory processes of duodenal ulcer, characteristic disturbances in gastric motor and secretory activities take place. It is concluded that persistent disturbances in the duodenal mechanism should arouse suspicion that a duodenal ulcer is not healed although symptoms may have disappeared and the roentgenograms may be normal.

Although these observations are of physiologic interest, it is the opinion of the reviewers that the procedures outlined are not practicable in the diagnosis of an active duodenal ulcer and are distinctly inferior to careful analysis of the symptoms and competent roentgen examination.

Differences Between Gastric and Duodenal Ulcer.—Hollander [213] discusses some of the clinical and physiologic differences between gastric and duodenal ulceration. He believes that Shay's theory accounts satis-

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212. Gershon-Cohen, J.: A Duodenal Mechanism Regulating the Motor and Secretory Activity of the Stomach, Radiology **48**:232-238, 1947.

213. Hollander, F.: Are Gastric Ulcer and Duodenal Ulcer Different Diseases? S. Clin. North America **27**:265-271, 1947.

factorily for the dissimilarities in secretory and motor response between patients with duodenal ulcer and those with gastric ulcer, i.e., the possible existence in the normal duodenum of one or two inhibitory mechanisms for the control of motor and secretory acidity of the stomach. Most patients with duodenal ulcer exhibit a considerable disturbance in these inhibitory mechanisms whereas patients with gastric ulcers do not. It is emphasized that the physiologic differences existing between gastric and duodenal ulceration are a consequence of the location of the lesion rather than a cause of it.

Rate of Healing.—The time required for the healing of the crater was studied by Cummings, Grossman and Ivy [214] in a series of 69 patients, 63 with duodenal ulcer and 6 with gastric ulcer, receiving milk and cream, a soft diet, an alkaline mixture of sodium bicarbonate and calcium carbonate and small amounts of phenobarbital and belladonna. Healing time was construed as the time interval between the original roentgen visualization of the crater and its subsequent disappearance. When the case in which two hundred and thirty days were required for "healing" is discounted, the average time was thirty-seven days for duodenal ulcer, with a range of thirteen to sixty-eight days, and forty-two days for gastric ulcer, with a range of eighteen to sixty-eight days. No correlation was found between the size of the crater and the rate of healing or between the age of the patient or the duration of symptoms and the time of healing. Pollard and his associates [215] noted considerable variation in the time required for the healing of craters in 100 cases of gastric ulcer.

Tobacco.—An investigation by Jamieson and others [216] of the smoking habits of 473 patients who recovered from perforation disclosed no evidence that an increase or a decrease in smoking influenced the severity of the symptoms.

Diabetes Mellitus and Peptic Ulcer.—Of 94 patients with both peptic ulcer and diabetes studied by Wood,[217] 59 had had diabetes for varying periods before the onset of ulcer symptoms; the remaining 35 had peptic ulcer first and later diabetes mellitus. The acidity seemed to be somewhat lower than the average for patients with ulcer. The following complications occurred in 62 of the 94 patients: 24 had gross or acute massive hemorrhage, and 8 had persistently positive reactions to tests for

214. Cummings, G. M., Jr.; Grossman, M. L., and Ivy, A. C.: A Study of the Time of "Healing" of Peptic Ulcer in a Series of Sixty-Nine Cases of Duodenal and Gastric Craters, Gastroenterology **7**:20-37, 1946.

215. Pollard, H. M.; Bachrach, W. H., and Block, M.: The Rate of Healing of Gastric Ulcers, Gastroenterology **8**:435-437, 1947.

216. Jamieson, R. A.; Illingworth, C. F. W., and Scott, L. D. W.: Tobacco and Ulcer Dyspepsia, Brit. M. J. **2**:287-288, 1946.

217. Wood, M. N.: Chronic Peptic Ulcer in Ninety-Four Diabetics, Am. J. Digest. Dis. **14**:1-11, 1947.

occult blood in the stool. Perforation occurred in 10, and retention was observed in 32, surgical intervention being necessary in 18.75 per cent of these. Advanced arteriosclerosis was present in most of those who had troublesome bleeding.

Size of Gastric Ulcer.—In a series of 384 patients with gastric ulcer the lesions measured more than 1.5 cm. in the longtitudinal axis in 41 per cent and more than 3 cm. in 6.5 per cent.[218] The relative incidence of larger ulcers increased with age. A high proportion of the larger lesions occurred in the body of the stomach, whereas smaller ulcers were found more often at the pyloric end.

Postbulbar Ulcer.—Sixteen cases of duodenal ulcers located beyond the bulb are reviewed;[219] in 75 per cent typical ulcer symptoms were present, and bleeding occurred in 37 per cent. The diagnosis was based on the roentgenologic findings except in 1 case, in which the condition was found surgically.

Kraemer [220] describes a 5 cm. duodenal ulcer located at the ampulla of Vater, with fatal hemorrhage from an erosion into the pancreaticoduodenal artery.

Hyperparathyroidism and Peptic Ulcer.—The coexistence of a healed duodenal ulcer, a healed jejunal ulcer and a pronounced clear cell hyperplasia of the parathyroid glands and primary hyperparathyroidism is described.[221] Death resulted from renal insufficiency secondary to nephrocalcinosis. Of interest is the fact that gastrointestinal symptoms presumed during life to be due entirely to the ulcer appeared in retrospect to have been manifestations of severe hyperparathyroidism. Two similar cases had been reported previously. All 3 patients had received large amounts of calcium and phosphorus in the diet. The authors suggest a possible relationship between long term ulcer therapy, with a high intake of milk, and the development of hyperparathyroidism. The reviewers have not encountered a case similar to the one described and consider the possibility most unlikely.

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218. Krisnapoller, N. H.: Röntgenologisches und Klinisches über das grosse Magengeschwür, Gastroenterologia **71**:142-170, 1946.

219. Falla Alvarez, L. and Farinnas, P. L.: Postbulbar Duodenal Ulcers, Gastroenterology **8**:1-14, 1947.

220. Kraemer, M.: Clinical Pathological Report, Gastroenterology **7**:687-691, 1946.

221. Rogers, H. M.; Keating, F. R., Jr.; Morlock, C. G., and Barker, N. W.: Primary Hypertrophy and Hyperplasia of the Parathyroid Glands Associated with Duodenal Ulcer, Arch. Int. Med. **79**:307-321 (March) 1947.

Pituitary Tumor and Peptic Ulcer.—Two patients with coexistent peptic ulcer and pituitary tumor are reported.[222] An intrasellar tumor was present in 1 patient; the other had acromegaly.

Medical Treatment.—The casual reader of therapeutic reports must be impressed by the fact that "good results" are almost always recorded. This is true in regard to the time-honored methods as well as to the newer procedures. Furthermore, the authors usually present a rational basis for the therapy used and one which is valid to them. The skeptic finds it difficult to reconcile the various concepts and is tempted to interpret the outcome as evidence of the natural cyclic cource of the disease or as the result of some unsuspected component mutual to the different procedures, such as suggestion and psychotherapy. In the opinion of the reviewers, the alleged "good results" must be critically analyzed, the natural history of the disease and the many facts which are known, as well as those still unknown, being borne in mind.

Gatewood [223] reemphasizes the need for individualization; the aggressive, hard driving businessman who is unsuited by temperament and occupation to a medical regimen may require surgical treatment; the patient in whom flare-ups are associated with emotional storms needs proper psychiatric attention, the person with an excessive night secretion may be best treated by means of vagotomy and patients with lesions not differentiated from carcinoma require gastroscopic study and laparotomy. The fundamental principle of the Sippy treatment is the control of free hydrochloric acid in the stomach throughout the day and night. The diet should be high in protein which has a high acid-combining value. Sodium bicarbonate is not recommended because of its tendency to disturb the acid-base equilibrium. The calcium compounds are advantageous because of their excellent neutralizing ability and of the relative rareness with which they cause untoward effects.

Tanner [224] considers rest in bed the most important factor. Recumbency diminishes gastric activity, decreases venous stasis, increases blood supply and even alters the acidity of the fluid bathing the ulcer on the lesser curvature. Gastrectomy is regarded as the ideal form of surgical treatment. The author attributes failure in 20 of his cases to the fact that despite objective signs of ulcer the ulceration was not the cause of symptoms.

Snorf [225] points out that complications constitute an intimate part of the life cycle of ulcer and influence the therapy.

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222. Wilson, H. T.; Olson, J. D., and Rivers, A. B.: Pituitary Tumors and Peptic Ulcers, Rev. Gastroenterol. **13**:371-373, 1946.

223. Gatewood, L. C.: Peptic Ulcer, M. Clin. North America **31**:10-112, 1947.

224. Tanner, N. C.: The Management of Peptic Ulcer, Bristol Med.-Chir. J. **63**:16-30, 1946.

Aluminum Hydroxide.—Thirty-two patients with ulcer were hospitalized and were subjected to a basic hospital regimen in which nonreactive aluminum hydroxide was used; 31 controls were treated similarly except that the reactive aluminum hydroxide was used.[226] The nonreactive form produced no greater clinical improvement than did the reactive form. No constant effect on gastric acidity was observed. The combination of collodial aluminum hydroxide gel and magnesium hydroxide is regarded by Jankelson as a more effective buffer in the stomach than collodial aluminum hydroxide gel alone.[227] Concretions of aluminum salts of fatty acids were noted.[228]

Resins.—On the basis of studies in rats fed diets containing "amberlite IR-4" for a period of eight months, Segal and his associates [229] conclude that the toxicity of the resin for rats is negligible. When it was given to 30 patients with peptic ulcer [230] all but 1 experienced relief of pain; healing occurred in some. Though the preparation has an unpleasant taste and nausea and vomiting sometimes occurred, no serious toxic effects were noted. Similar results are reported by Kraemer and Lehman.[231] The advantage of this preparation over the effective, inexpensive antacid, calcium carbonate, remains to be established, in the opinion of the reviewers.

Protein Hydrolysates.—Protein hydrolysate was given to 134 patients in the amount of 0.6 Gm. per kilogram of body weight.[232] The remainder of the diet was composed of "dextri-maltose" so as to afford 40 to 50 calories per kilogram. The mixture was dissolved in water and divided into eight feedings. After a two week period without pain, food was substituted for one hydrolysate feeding; a normal bland diet was

225. Snorf, L. L.: The Influence of Complications on the Treatment of Peptic Ulcer, Am. Pract. **1**:401-408, 1947.

226. Smith, F. H.: Nonreactive Aluminum Hydroxide in the Treatment of Peptic Ulcer, Gastroenterology **8**:494-503, 1947.

227. Jankelson, I. R.: Colloidal Aluminum Hydroxide Gel and Magnesium Hydroxide in the Management of Peptic Ulcers, Am. J. Digest. Dis. **14**:11-12, 1947.

228. Child, G. P.; Hall, W. K., and Averbach, S. H.: The Formation of Concretions of Aluminum Salts of Fatty Acids After the Use of Aluminum Hydroxide, Am. J. Digest. Dis. **14**:63-64, 1947.

229. Segal, H. L.; Hodge, H. C.; Watson, J. S., and Coates, H.: A Polyamine Formaldehyde Resin: III. Chronic Toxicity Experiment in Rats, Gastroenterology **8**:199-201, 1947.

230. Spears, M. M., and Pfeiffer, M. C. J.: Anion Exchange Resin and Peptic Ulcer Pain, Gastroenterology **8**:191-198, 1947.

231. Kraemer, M., and Lehman, D. J., Jr.: The Treatment of Peptic Ulcer with Anion Exchange Resins, Gastroenterology **8**:202-204, 1947.

subsequently resumed gradually. Satisfactory results are reported for 118 patients. Of the 16 who did not improve, 2 had hemorrhage and 2 had perforation.

Thirteen patients with duodenal ulcer, 1 with gastric ulcer and 1 with combined duodenal and gastric ulcer were given 1,500 cc. of a 6 per cent solution of protein hydrolysate daily for an average of nine days.[233] Roentgenograms showed that the ulcer disappeared in 9 cases and was decidedly improved in 5; 1 patient failed to respond. Twenty-six patients with ulcer treated with protein hydrolysate for a two to three week period experienced a satisfactory remission.[234] The frequency of relapses was not diminished, however. Changes in the serum protein and hemoglobin levels were inconsistent. The beneficial effects of protein hydrolysate are ascribed to its buffering action and to the increased nitrogen intake. It should be pointed out that despite various clinical reports on the efficacy of amino acid preparations in the management of peptic ulcer there is no conclusive evidence as yet that a protein deficiency uniformly occurs in the patients or that protein hydrolysates are therapeutically superior to the standard antacid regimen.

Parenteral Therapy.—Faroy and his associates [235] obtained satisfactory results in the "control" of acute peptic ulcers after injection of milk proteins intravenously.

Satisfactory results are recorded in the treatment of peptic ulcer by the combined use of "larostidin" (histidine monohydrochloride), an extract of the gastroduodenal mucosa and the program of Meulengracht.[236] The authors add that antispasmodics, sedatives and absorbent powders are important adjuncts in treatment.

Bernstein [237] treated 75 patients with peptic ulcer with an average of twenty daily injections of 0.2 mg. of histamine diphosphate. Fifty pa-

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232. Ruggiero, W. F.; Co Tui, and Bianco, A. A.: The Management of Ambulatory Peptic Ulcer Patients with Protein Hydrolysates, New York State J. Med. **46**:2395-2398, 1946. Co. Tui: The Ambulatory Treatment of Peptic Ulcers with Protein Hydrolysates and Dextri-Maltose, Rev. Gastroenterol. **14**:108-128, 1947.

233. Kimble, S. T.: A Preliminary Report on Protein Hydrolysate Therapy for Peptic Ulcer, Gastroenterology **8**:467-475, 1947.

234. Hodges, H. H.: Protein Hydrolysate Therapy for Peptic Ulcer: Report of Twenty-Six Cases, Gastroenterology **8**:476-493, 1947.

235. Faroy, G.; Arnous, J., and Fénéon, J.: Treatment of Gastroduodenal Ulcers with Intravenous Injection of Milk Proteins, Presse méd. **55**:313-314, 1947.

236. Pulver, W., and Meier, H.: Vergleichende Beobachtungen Zwischen der Larostidin-, Robuden- und der diätetischen Behandlung der Ulcera ventriculi et duodoni, Schweiz. med. Wchnschr. **76**:1151-1153, 1946.

237. Bernstein, B. M.: Histamine in the Treatment of Peptic Ulcer, Ann. Int. Med. **26**:852-857, 1947.

tients (66 per cent) were apparently relieved of pain after the fourth injection; 82 per cent were relieved after the tenth injection. Five patients did not respond; in 1 fatal perforation and hemorrhage developed during treatment, and another had a perforation soon after the histamine injections were begun. Twenty-six patients were considered to have been protected against an anticipated recurrence. The reviewers are not impressed by the evidence presented in this and in preceding reports on parenteral therapy. It is pertinent to recall the apparently "beneficial" effects reported after the use of isotonic solution of sodium chloride and of distilled water given parenterally.

Enterogastrone.—Greengard and his associates [238] describe a method for the preparation of an enterogastrone concentrate of uniform potency and suitable for parenteral injection in man. Twenty-five Mann-Williamson dogs were treated with 150 mg. of an enterogastrone concentrate daily. Fifteen animals died within the twelve month period of injection, 8 from ulcer and 7 from other causes, and 10 remained free of ulcers during the treatment period. One died of perforation twenty-eight months after treatment, 8 died from miscellaneous causes eleven to forty-eight months after treatment and at autopsy were found to be free of ulcers and 1 is still living five years after treatment. The 10 dogs given control injections of pork muscle extract all died of ulcer in an interval similar to that observed for the untreated Mann-Williamson animals. Eight dogs were treated with the more highly purified concentrate given intramuscularly in one daily 100 mg. dose. Three died within the twelve month period, 1 from ulcer and the other 2 from extraneous causes; of the 5 remaining animals, 3 died from causes other than ulcer fourteen to eighteen months after cessation of therapy; 1 is living and is in excellent condition despite the fact that for three years ulcer therapy was not applied and 1 died of a perforated ulcer after two and a half years. Carefully selected patients with a history of ulcer for five years or more were treated with 200 mg. of enterogastrone. Thirty-two were treated three times a week and 26 six times a week; all were treated for a year except 30. The patients were allowed a modified ulcer diet and antacids for the control of pain; follow-up was made three to four times a year after treatment. The results to date suggest that enterogastrone is effective in preventing recurrences during the treatment period and for an unestimated length of time after discontinuance of the treatment. Pain at the site of the injection was an undesirable but not an intolerable reaction. Vasodepressor reactions were noted in dogs and in 2 patients in

238. Greengard, H.; Atkinson, A. J.; Grossman, M. I., and Ivy, A. C.: The Effectiveness of Parenterally Administered "Enterogastrone" in the Prophylaxis of Reccurrences of Experimental and Clinical Peptic Ulcer, Gastroenterology **7**:625-649, 1946.

whom a gluteal vein was accidentally entered. Urticaria developed in 3 patients sensitive to pork. The mechanism of the protection is not known, but apparently it is not due to an inhibition of gastric secretion. Hubacher [239] reports beneficial results from the use of Swiss-made gastric and intestinal extracts in 44 of 54 cases. Follow-up studies extended over sixteen months. A rapid decrease in the size of the crater was noted in the patients favorably affected. Patients were given twelve to twenty-one injections either daily or three times a week. At the same time tablets containing the water-insoluble portions of the extracts were given orally. Gastric acidity values before and after therapy are not recorded. Surkes [240] reviews observations on 92 patients with gastroduodenal ulcer treated with extracts from the gastrointestinal mucosa. The preparations were administered both by intragluteal injection and orally. "Favorable results" are reported for 82 per cent of the patients with gastric ulcer and for 92 per cent of the patients with duodenal ulcer.

It is clear that the use of enterogastrone and other extracts in the treatment of peptic ulcer is still distinctly in the experimental stage, with little likelihood of their proving of great value therapeutically unless much more potent and at the same time less irritating preparations can be obtained.

Massive Hemorrhage.—Jones [241] discusses in detail the various causes of bleeding from the gastrointestinal tract and their management; this article can be read with profit for its comprehensive and logical approach.

Among 140 patients with hemorrhage reviewed by Wilkinson and Tracey,[242] gross hemorrhage constituted the first symptom of ulcer in 70; only 1 of these died from the original hemorrhage, and 2 died from subsequent hemorrhages. Sixty patients had but one gross hemorrhage; 78 per cent of these responded well to medical treatment. Seventy-four had had more than one hemorrhage before their admission to the hospital; of these, only 25 per cent responded to medical management and had no recurrent hemorrhages. Sixty-one per cent were subjected to operation; hemorrhage recurred after surgical intervention in one third of this group. Forty-one patients of the entire series underwent subtotal gastrectomy; hemorrhage recurred after surgery in 24 per cent of this group.

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239. Hubacher, O.: Peptic Ulcer with Gastric and Intestinal Extracts, Lancet **2**:272-274, 1946.

240. Surkes, A. W.: Internal Treatment of Gastric and Duodenal Ulcer, Schweiz. med. Wchnschr. **77**:455-458, 1947.

241. Jones, C. M.: Diagnostic and Therapeutic Considerations of Gastrointestinal Bleeding, New England J. Med. **235**:773-776, 1946.

242. Wilkinson, S. A., and Tracey, M. L.: The History of Hemorrhage in Peptic Ulcer, Gastroenterology **7**:450-455, 1946.

One hundred and twenty-four patients were treated medically, with recurrent bleeding in 30 per cent. Of 16 patients operated on without previous medical treatment, 25 per cent suffered subsequent hemorrhage. Wilkinson and Tracey suggest that although recurrent hemorrhages will develop in about 25 per cent of patients regardless of the type of treatment medical management will prevent recurrence of bleeding in many patients with a history of but one previous episode. However, if multiple hemorrhages have occurred, subtotal gastrectomy is the procedure of choice. This analysis indicates that the first hemorrhage is not so likely to be fatal as are subsequent ones, that patients with multiple hemorrhages do not respond well to medical management and that even radical operations are far from satisfactory in preventing recurrent hemorrhage.

Of 295 patients with gastrointestinal bleeding treated at Los Angeles County General Hospital during the year 1944, 142 had peptic ulcer.[243] Hematemesis was the presenting symptom in 111 of these, and melena was the presenting symptom in the other 31. A clinical diagnosis of esophageal varices was made in 85 of the 153 cases of hematemesis from causes other than ulcer; the mortality was 58.8 per cent. In the remaining 68 cases the bleeding was variously attributed to gastric carcinoma, gastritis, lesions of the small bowel, poisons, metabolic disturbances and unknown causes (6 cases). Schatzki[244] advocates early roentgen examination of patients with gastrointestinal bleeding because of the obvious advantage of an early precise diagnosis of the cause and location of the bleeding. The examination is made without abdominal palpation and with the patient in the horizontal position, peristalsis and gravity (turning the patient from side to side) being used as the means of distributing the barium over the surface of the esophagus, stomach and duodenum.

Roentgen studies of 18 patients three months after their recovery from acute hematemesis revealed a chronic duodenal ulcer in 5, gastric ulcer in 1 and an anastomotic ulcer in 1.[245] Two patients gave a history suggestive of ulcer; no roentgen evidence of ulceration was obtained, and the correct diagnoses for 1 proved to be cirrhosis of the liver and for the other hypertension with severe epistaxis. Six patients gave no history of digestive disturbances, and in the absence of positive findings the hemorrhage was attributed to acute gastric erosions. In one report[246] massive hemorrhage is attributed to ulceration of the mucosa overlying aberrant pancreatic tissue.

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243. Thompson, H. L.; Oyster, J. M.; Heid, J. B., and Morgan, F. M: Hematemesis; A Study of Underlying Causes, Gastroenterology **7**:320-331, 1946.

244. Schatzki, R.: Roentgenologic Examination in Patients with Bleeding from the Gastro-Intestinal Tract, New England J. Med. **235**:783-786, 1947.

245. Cluer, E. H.: Evidence of Ulcer in Hematemesis, Brit. M. J. **2**:651, 1946.

246. Chapman, B. M.; Vogel, W. F., and Schomaker, T. P.: Massive Gastric Hemorrhage Associated with Aberrant Pancreas in the Stomach, Gastroenterology **8**:367-374, 1947.

Massive gastrointestinal bleeding arose in 4 children from a Meckel diverticulum, duplication of the terminal ileum, a polyp of the descending colon and a bleeding duodenal ulcer respectively; the ulcer occurred in a 12 year old boy.[247] Schrumph[248] discusses the mechanisms of early and late azotemia.

Among 337 patients hospitalized because of massive hemorrhage from peptic ulcer the mortality rate was 10 per cent for patients operated on early (within forty-eight hours of onset) and 70 per cent for those operated on late (more than forty-eight hours after onset).[249] Large amounts of blood administered as transfusions before, during or after operation were of great value in operations performed for the control of hemorrhage. In the differentiation of fatal and nonfatal types of hemorrhage, the most consistent criteria were failure to improve promptly under a strict regimen of rest in bed, moderate doses of morphine, the withholding of fluids and food by mouth and adequate blood transfusions and the recurrence of hemorrhage.

In a series of 539 patients with hemorrhage due to ulcer treated from 1929 to 1945 the operative mortality decreased from 45 per cent before 1939 to 7 per cent after 1939 and the mortality rate among patients treated medically diminished from 6 to 5 per cent; this was a total decrease in mortality from 9.1 to 5.1 per cent.[250] The improved results are attributed to a better understanding of the nutritional requirements and to the more effective control of shock. Zinninger[251] recommends that patients with known gastric or duodenal ulcer who bleed seriously while under treatment be operated on promptly, either during or immediately after hemorrhage. Patients with a gastrojejunal ulcer who continue to bleed may require surgical treatment. Operation is indicated also for persons with perforation or obstruction in addition to bleeding and for those with repeated severe hemorrhages. The type of operation varies with the individual case, but partial gastrectomy is the procedure of choice whenever possible. Ligation of the vessels around the ulcer may be desirable.

Pyloric Obstruction.—Sixty of 72 patients (83 per cent) with pyloric obstruction secondary to peptic ulcer were treated successfully by a conservative regimen comprising gastric lavage with sodium bicarbonate, a

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247. Donovan, E. J.: Gross Intestinal Hemorrhage in Infants and Children, S. Clin. North America **27**:443-446, 1947.

248. Schrumpf, A.: Azotemia in Gastro-Intestinal Hemorrhage, Am. J. Digest. Dis. **14**:169-170, 1947.

249. Heuer, G. J.: The Surgical Aspects of Hemorrhage from Peptic Ulcer, New England J. Med. **235**:777-783, 1946.

250. Bohmansson, G.: Surgical Arrest of Massive Hemorrhage, Acta chir. Scandinav. **94**:362-378, 1946.

251. Zinninger, M. M.: The Surgical Treatment of Bleeding Peptic Ulcer, S. Clin. North America **26**:1140-1151, 1946.

six meal diet, antispasmodics and an aluminum hydroxide preparation. Surgical intervention is indicated if there is no improvement after a period of ten days.[252]

Acute Perforation.—Crohn, Rouse and Smith [253] discuss the various legal aspects of the relationship between trauma and perforation.

Of 166 patients with acute perforation, 95.8 per cent were males.[254] The chief physical findings were abdominal tenderness (97 per cent), abdominal rigidity (95 per cent), absent peristaltic sounds (73 per cent), subnormal body temperature (68 per cent) and diminished hepatic dulness (65 per cent). The onset of epigastric pain was sudden in 97 per cent of the cases, and bleeding occurred in 13 per cent. A definite or suggestive history of peptic ulcer was obtained in 73 per cent. For the 138 patients treated surgically the mortality was 21 per cent; for the 28 treated medically the mortality was 41 per cent. The diagnosis was established in 11 cases at autopsy. The high mortality rate is attributed to (*a*) poor nutrition and poor general condition of the charity patients and (*b*) the variety of operators of varying skill as well as to poor postoperative treatment in some cases. It is recommended that the general condition of the patient be improved by suction, transfusions and infusions of plasma and fluid before operation, even if surgical intervention is delayed a few hours.

Of 20 men with perforation of a peptic ulcer in the service who were observed for a sufficiently long period, 12 were returned to full duty and 3 to limited duty, without subsequent disability for periods ranging from seven months to two and a half years.[255] Interestingly, all perforations occurred shortly after the men were inducted into service; in 14 instances they occurred between seven days and two months after induction. Perforation of a duodenal ulcer occurred during roentgen examination, with spreading of barium throughout the abdominal cavity.[256] In an instance of retroperitoneal perforation of an ulcer on the posterior wall of the duodenum roentgen films demonstrated extravasated air along the crus of the left hemidiaphragm, between the peritoneum and the muscle layer of the diaphragm, and air over the superior pole of the left kidney.[257] A

252. Seeley, S. A.: Medical Management of Pyloric Obstruction Resulting from Peptic Ulcer, Am. J. Digest. Dis. **13**:238-243, 1946.

253. Crohn, B. B.; Rouse, O., and Smith, H. W.: The Relationship of Trauma to the Perforation of Peptic Ulcer, Gastroenterology **7**:456-463, 1946.

254. Olson, H. B., and Norgore, M.: Perforated Gastroduodenal Ulcers: A Study of One Hundred and Sixty-Six Cases, Ann. Surg. **124**:479-491, 1946.

255. Lynns, S. C., and Sinclair, L. G.: Perforated Peptic Ulcers in Naval Personnel, South. M. J. **39**:575-580, 1946.

256. Schilling, J. A.: Perforation of a Duodenal Ulcer During Roentgen Examination, Surgery **20**:730-745, 1946.

257. Koenig, E. C., and Culver, G. J.: Retroperitoneal Perforation of the Duodenum, Radiology **48**:164-167, 1947.

perforated duodenal ulcer in a boy 14½ years old was treated successfully by subtotal resection of the stomach.[258]

Taylor [259] treated a consecutive series of twenty-eight perforations by gastric aspiration instead of operation; the treatment was based on his observation that early perforations seal themselves if the stomach is emptied and kept empty by aspiration and, further, that gastric contents in the peritoneal cavity will be sterilized and absorbed if the leakage is not gross and the contamination not repeated. Twenty-four of the 28 patients recovered. Of the 4 who died, the outcome in 3 was considered as not related to the method of treatment.

Fourteen consecutive patients with acute perforation were treated conservatively by Visick [260] with morphine, intermittent gastric suction and intravenous administration of sulfathiazole and fluid. The temperature returned to normal in six to eight days. Abdominal rigidity gradually lessened, and it disappeared in two to three days. Pain was relieved in one hour, and it did not return except in 2 cases. Eleven patients recovered completely, 2 died, 1 of pneumonia and 1 of subphrenic abscess, and a third recovered eventually after drainage of a subphrenic abscess which had developed. It is concluded that if the perforation is small and spillage negligible, spontaneous closure, with recovery, may well occur. It should be noted also that among patients with acute perforation the surgical mortality is low. Despite these interesting and encouraging results, the reviewers still regard prompt surgical intervention as the treatment of choice, although Graham [261] permits delay for adequate preoperative preparation.

Kingsbury and Schilling,[262] from a study of 224 consecutive cases, report a total mortality of 13.4 per cent, with an operative mortality of 12.6 per cent. Peritonitis was the chief cause of death. There was a mortality of only 5.1 per cent in the group operated on within six hours of the onset of symptoms. Six and two-tenths per cent of the patients gave a history of one or more previous perforations.

Baritell [263] records a mortality of only 1.1 per cent from a series of eighty-eight consecutive operations for perforated gastroduodenal ulcer.

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258. Orlov, M.: Perforated Ulcer in a Child: Report of a Case, West. J. Surg. **55**:326-328, 1947.

259. Taylor, H.: Perforated Peptic Ulcer Treated Without Operation, Lancet **2**:441-444, 1946.

260. Visick, A. H.: Conservative Treatment of Acute Perforated Peptic Ulcer, Brit. M. J. **2**:941-944, 1946.

261. Graham, R. R.: The Treatment of Acute Perforation of Duodenal Ulcer, Am. J. Surg. **72**:802-810, 1946.

262. Kingsbury, H. A., and Schilling J. A.: Acute Perforation of Peptic Ulcer: Early and Late Results, New York State J. Med. **47**:372-376, 1947.

263. Baritell, A. L.: Perforated Gastroduodenal Ulcer, Surgery **21**:24-33, 1947.

On the basis of an analysis of 200 cases, Johansson [264] finds the prognosis between six and twenty-four hours after perforation now relatively good for patients under the age of 40. The outlook is extremely poor in regard to perforations of more than one day's duration even for young patients; it is considerably worse for women than for men.

In a follow-up study [265] of 244 patients treated by simple suture, 65 per cent reported further symptoms; of these, 33 per cent required further surgical intervention.

Werbel and others [266] found that in 41 per cent of patients recovering from the perforation of a nonresected ulcer symptoms requiring hospitalization subsequently developed. A second perforation occurred in 17 per cent, and 30 per cent required additional gastric operations.

The clinical picture in a 53 year old man with a gastrocolic fistula who had undergone repair of a perforation and a gastroenterostomy fifteen years earlier was that of a severe nutritional deficiency.[267]

Surgical Treatment.—The literature on gastric surgery for 1945 is reviewed by Marshall and Schmidt.[268] The numerous papers on subtotal gastrectomy reflect the current popularity of this procedure. In general, the mortality rate has decreased, with the result that the indications for operation have been extended; it is considered indicated primarily in cases of gastric ulcer in which the possibility of malignancy cannot be excluded,[269] and in cases of ulcers with cicatricial stenosis, massive hemorrhage and "intractable pain." These symptoms were found by Thompson [270] in 40 of 50 unselected patients subjected to elective operation. Late results of subtotal gastrectomy are difficult to ascertain. Allen and Welch,[271] in a follow-up study of 136 patients who had survived subtotal gastrectomy for duodenal ulcer, found that, with the exclusion of the cases in which Finsterer resections were carried out (failure occurred in

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264. Johansson, O.: 200 Fälle von perforierenden Magen und Duodenalgeschwüren, Acta chir. Scandinav. **95**:233-259, 1947.

265. Houston, W.: The Aftermath of Perforated Peptic Ulcer, Brit. M. J. **2**:221-223, 1946.

266. Werbel, E. W.; Kozoll, D. D., and Meyer, K. A.: Surgical Sequelae Following Recovery from a Perforated Peptic Ulcer, S. Clin. North America **27**:93-108, 1947.

267. Ruffin, J. M., and Margolis, G.: Clinical Pathological Conference, Gastroenterology **7**:118, 1946.

268. Marshall, S. H., and Schmidt, I. C.: Gastric Surgery: A Review of Literature for 1945, Gastroenterology **8**:160-174, 1947.

269. Hinton, J. W.: Indications for Surgery in the Treatment of Gastric and Duodenal Ulcers, Bull. New York Acad. Med. **22**:623-629, 1946.

270. Thompson, H. L., and Prout, H.: Surgical Treatment of Peptic Ulcer, Arch. Surg. **54**:390-413 (April) 1947.

271. Allen, A. W., and Welch, C. E.: Subtotal Gastrectomy for Duodenal Ulcer, Ann. Surg. **124**:688-707, 1946.

6 of 7), the late effects were excellent in 87 per cent, "improved" in 6 per cent, and definitely poor in 7 per cent. There were three anastomotic ulcers in the last group, one of which developed ten years after resection. Bartels and Dulin,[272] from a study of 221 consecutive cases, report a reduction in the mortality rate from 28 to 8 to 1.6 per cent, accompanied with a reduction in the rate of recurrence from 14.7 to 1.89 per cent. Miller and Nicholson report similar observations.[273]

Watson [274] attributes most of the bad results to inadequate resection and to the use of an excessively long loop, there being evidence that the shorter the loop the greater the safety from ulceration. Steinberg [275] also found that the standard radical proximal short loop, retrocolic terminolateral gastrectomy with a sufficiently wide stoma, gave maximum protection against jejunal ulcers. There have been numerous publications dealing with gastric resection in the Belgian literature.[276]

Palliative gastric resection, introduced by Florcken in 1928, consisting of subtotal resection distal to the ulcer, is, according to Colp and Druckerman,[277] applicable to (1) juxtaesophageal ulcers and peptic ul-

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272. Bartels, R. N., and Dulin, J. W.: Gastric Resection for Peptic Ulcer: A Study of Two Hundred Twenty-One Consecutive Cases, Surgery **21**:496-511, 1947.

273. Miller, T. G., and Nicholson, J. T. L.: Results from Subtotal Gastric Resection in Peptic Ulcer, Am. J. Med. **1**:476-484, 1946.

274. Watson, A. B.: Partial Gastrectomy for Simple Ulcer: Review of End Results of One Hundred and Thirty-Two Cases, with Criticism of Polya Operation, Brit. J. Surg. **34**:353-366, 1947.

275. Steinberg, M. E.: Treatment of Recurrent Peptic Ulcers Following Gastric Operations, Northwest Med. **46**:114-125, 1947; Reoperative Surgery for Recurrent Peptic Ulcerations, Surg. Gynec. & Obst. **84**:1029-1037, 1947.

276. Gallart-Mores, F.: Commentaire sur la pathologie du gastrectomisé pour ulcère, d'apres notre statistique, Acta gastro-enterol. belg. **9**:215-218, 1946. Van Goidsenhauen, F.; Appelmans, R.; Hendrichx, M.; Jooseens, J.; Vaylsteke, A., and Staessen, A.: Les suites eloignées de la gastrectomie subtotale du point de vue clinique, ibid. **9**:254-299, 1946. DeWitte, F.: Les suites precoses et tardives de la gastrectomei du point de vue radiologique, ibid. **9**:303-318, 1946. Delayers, L.: Physiopathologie de la gastrectomie subtotale pour ulcère, ibid. **9**:318-350, 1946. Goffaerts, A., and others: La gastrectomie du point de vues chirurgica¹: Resultats de la gastrectomie (deux tiers); dans le traitement de l'ulcère gastroduodenal, ibid. **9**:408-430, 1946. Goedsels, L., and Verdoodt, F.: Les suites precoces et tardives de la gastrectomie, ibid. **9**:431-440, 1946. Warmoes, F., and Cllewaert, R.: Note sur l'interet de la gastroscopie dans le diagnostic des troubles après gastrectomie, ibid. **9**:440-442, 1946. Froehlich, A., and Saln, J.: Syndrome d'enterite grave après gastrectomie: lambliase akranglo resistante, ibid. **9**:442-445, 1946. Godart, J., and Van Leroberghe, L.: Insuffisance hepatique consecutive a la gastrectomie, ibid. **9**:453-455, 1946. Massion, J.: Sur les suites de la gastrectomie pour ulcère, ibid. **9**:458-459, 1946. Van Hee, J.: Les suites precoces de la gastrectomie, ibid. **9**:460, 1946.

277. Colp, R., and Druckerman, L. J.: Palliative Gastrectomy in Selected Cases of Gastric Ulcer, Ann. Surg. **124**:675-687, 1946; A Rational Approach to the Surgery of High Gastric Ulcer, S. Clin. North America **127**:231-240, 1947.

cers of the esophagus, (2) ulcers high in the lesser curvature and (3) penetrating ulcers on the posterior wall of the cardia in patients whose general physical condition does not warrant removal of the ulcer. Eight patients were subjected to this procedure, with one postoperative death, presumably due to coronary thrombosis. The remaining 7 were observed for periods ranging from twenty-one months to eight years. Absence of free hydrochloric acid was noted in test meals. All gained weight and were free from gastric symptoms. One patient died from uremia twenty-one months after operation; a healed gastric ulcer was demonstrated at autopsy. Roentgen and gastroscopic studies on the remaining 6 patients gave no evidence of the lesion.

Fallis and Warren[278] favor surgical treatment of jejunal ulcers after a trial of intensive medical therapy. Delannay[279] stresses the importance of adequate resection of the stomach and of the removal of the entire duodenal bulb. The reviewers agree on the desirability of a sufficiently wide resection, but they are not convinced on the value of so-called denudation of the mucosa of the antrum and the duodenal bulb. In a case observed recently, after partial gastrectomy and apparently thorough removal of the mucosa of the antrum and the first portion of the duodenum the twelve hour nocturnal gastric secretion measured approximately 2,000 cc., with a free acidity of 100 clinical units!

Hypoglycemia After Gastric Resection.—Intense fatigue several hours after eating in patients who have undergone either a total or a partial gastric resection has been attributed by Conn [280] to postprandial hypoglycemia. The reaction to the oral dextrose tolerance test is characterized by a rapid rise of the normal fasting blood sugar content to hyperglycemic levels during the first hour and a precipitous fall to hypoglycemic levels between the second and fourth hours. A high protein, low carbohydrate diet has given excellent results. A similar conclusion is reached by Adlersberg and Hammerschlag,[281] whose patients complained of fulness, nausea, dizziness, palpitation, sweating, headache, fatigue and weakness appearing two to four hours after meals.

Perman [282] recommends disconnection of the gastrojejunal anastomosis and the establishment of an end to end gastroduodenal anastomosis

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278. Fallis, L. S., and Warren, K. W.: Surgical Treatment of Jejunal Ulcer, Am. J. Surg. **72**:4-11, 1946.

279. Delannay, E.: Peptic Ulceration After Gastrectomy, Mém. Acad. de chir. **72**:386-388, 1946.

280. Conn J. W.: The Diagnosis and Management of Spontaneous Hypoglycemia, J.A.M.A. **134**:130-138, (May 10) 1947.

281. Adlersberg, D., and Hammerschlag, E.: Postgastrectomy Syndrome, Surgery **21**:720-729, 1947.

282. Perman, E.: The So-Called Dumping Syndrome After Gastrectomy, Acta med. Scandinav. (Supp. 196) **128**:361-365, 1947.

for patients with symptoms of the "dumping" syndrome after gastrectomy. This procedure was carried out in 25 cases, with 1 death from peritonitis. Recurrence of an ulcer in the duodenum was observed in 1 case.

Vagotomy.—Dragstedt [283] reemphasizes the importance of acid gastric juice in the pathogenesis of peptic ulcer and describes experiments on completely isolated stomachs secreting large amounts of highly acid gastric juice (1 to 2 liters in twenty-four hours). Typical peptic ulcers frequently appear unless the vagus nerves have been divided. It seems likely that the absence of ulcers in the isolated stomachs after vagus section is due to the greatly diminished secretion characteristic of the animals. Thus in 1 animal the secretion fell from an average of 1,100 cc. per twenty-four hours for a two week period, with a free acidity of 116 clinical units, to an average of 410 cc., with a free acidity of 30 units, after vagal section. A second animal secreted an average of 500 to 800 cc., with a free acidity of 33 to 90 units, before vagotomy; this was reduced to 40 to 100 cc., with a free acidity of 0 to 12 units, after the vagal section. These experimental observations are important in view of the evidence that an excessive continuous secretion of gastric juice occurs in most patients with peptic ulcer. The relief of distress from ulcer following vagotomy is attributed chiefly to the striking reduction in acidity, although the reduction in tonus and in motility of the stomach is also important in that it reduces the exposure of the ulcer to peptic digestion and irritation. Complete division of the vagus nerves results in prompt healing of gastric, duodenal and gastrojejunal ulcers. The healing of gastrojejunal ulcers is particularly impressive. A gastroenterostomy in addition to the vagal section was performed in 62 of 122 patients with duodenal ulcer; no recurrent or stomal ulcers developed in this group.

Healing occurred after supradiaphragmatic section of the vagus nerves in all of 10 patients with gastrojejunal ulcer.[284] The relief of distress uniformly obtained by means of vagotomy was not due to anesthesia of the stomach, since reappearance of typical ulcer pain could be immediately induced in sensitive subjects by the postoperative instillation of acid into the stomach. Ruffin and others,[285] on the other hand, failed

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283. Dragstedt, L. R.: Some Physiological Principles in Surgery of the Stomach, Canad. M. A. J. **56**:133-137, 1947.

284. Dragstedt, L. R.; Clarke, J. S.; Harper, P. V.; Woodward, E. R., and Tovee, E. B.: Supradiaphragmatic Section of the Vagus Nerves to the Stomach in Gastrojejunal Ulcer, J. Thoracic Surg. **61**:226-236, 1947.

285. Ruffin, J. M.; Grimson, J. S., and Smith, R. C.: The Effect of Transthoracic Vagotomy upon the Clinical Course of Patients with Peptic Ulcer, Gastroenterology **7**:599-606, 1946. Ruffin, J. M., and Smith, R. C.: The Treatment of Peptic Ulcer with Special Reference to Vagotomy, Am. Pract. **1**:118-134, 1947.

to produce pain by the introduction of acid into the stomach after transthoracic vagotomy and hence associate the relief from pain with the decreased motility. The reviewers have themselves repeatedly produced pain after transthroracic vagotomy by the injection of acid solutions into stomachs containing sensitive jejunal ulcers; hence, the pain pathways are intact, and the normal stimulus of acid may be adequate to evoke pain. The decreased motility after vagal section doubtless serves to lessen the acid attack, hasten the process of healing and raise the pain threshold more or less rapidly to the point of insensitivity.

Transthoracic vagotomy was followed by healing or quiesence of gastric, duodenal or marginal ulcers in 56 of 57 cases reported by Grimson and others.[286] After vagotomy, 40 patients experienced an uncomfortable fulness of the stomach, and 28 described swelling or distention of the abdomen. Temporary difficulty in swallowing was noted by 21 and colicky abdominal pain by 38. In 31 cases there was an excessive passage of gas through the rectum; temporary diarrhea developed in 20. The average volume of the nocturnal gastric secretion was reduced in 32 cases from 888 to 340 cc. Reduction of the amplitude of gastric contraction, as judged by balloon study, occurred more consistently than reduction of acidity.

The clinical and laboratory data on a group of 40 such patients were studied by Moore and his associates.[287] The clinical results were good, with healing of the ulcer and no recurrences. Transient, undesirable side effects occurred in about 10 per cent. The fasting acidity and motility gradually returned to normal after one year. The secretory response to insulin-induced hypoglycemia remained abolished in most cases, and the clinical well-being of the patients also appeared to outlast the duration of the early changes in secretion and motility. Similar satisfactory results are reported from the treatment of gastrojejunal and duodenal ulcer by supradiaphragmatic vagotomy[288] and also from treatment by the subdiaphragmatic approach.[289]

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286. Grimson, K. S.; Baylin, G. J.; Taylor, H. M.; Hesser, F. H., and Rundles, R. W.: Transthoracic Vagotomy: The Effects in Fifty-Seven Patients with Peptic Ulcer and Clinical Limitations, J.A.M.A. **134**:925-932 (July 12) 1947.

287. Moore, F. D.; Chapman, W. P.; Schulz, M. D., and Jones, C. M.: Resection of the Vagus Nerves in Peptic Ulcer, J.A.M.A. **133**:741-748 (Marc 15) 1947.

288. Weinstein, V. A., and Colp, R.: Supradiaphragmatic Vagotomy in Gastrojejunal Ulceration Following Subtotal Gastrectomy for Duodenal Ulcer, S. Clin. North America **27**:249-253, 1947. Wulff, H.: Supradiafragmal bilateral vagotomi vid ulcus duodeni sine ventriculi, Nord. med. **21**:1226-1228, 1947.

289. Crile, G., Jr.: Subdiaphragmatic Vagotomy: Indications and Technic, Cleveland Clin. Quart. **14**:65-75, 1947.

The subcutaneous administration of 10 mg. of urethane of B-methyl choline in a patient with considerable gastric retention after vagotomy led to the restoration of gastric peristalsis and motility and relief of the epigastric distress.[290] Subsequently, oral and sublingual administration of the drug had a similar effect. In another vagotomized patient parenteral administration induced sufficient gastric tonus and peristalsis as well as pyloric relaxation. Strong peristaltic waves noted after five to ten minutes lasted for about forty minutes and could be abolished by the parenteral administration of 0.8 mg. of atropine sulfate. The secretion of acid was also increased.

Hollander [291] describes a physiologic test for the presence of uncut vagal fibers based on the fact that hypoglycemia centrally stimulates vagal activity and thereby increases gastric secretion. The test has proved useful, but the reviewers venture to suggest that a negative result may be obtained, at least temporarily, in the presence of an incomplete section of the nerves.

DUODENUM

Anatomic Variations.—Friedman [292] studied the position of the duodenum in roentgenograms of approximately 450 patients with a normal alimentary tract. The mean location of the highest point of the first portion of the duodenum was opposite the lower part of the second lumbar vertebra; the position varied between the third and twelfth lumbar vertebrae. The variation was found to be due in part to a downward migration with age of the duodenal high point at a statistical rate of almost half a vertebra per decade. The mean position of the lowest point of the third part of the duodenum was opposite the interspace between the third and fourth vertebrae, the position varying between the second and fifth vertebrae. The third part of the duodenum does not migrate downward with age so that there is a constant tendency toward shortening of the vertical diameter of the duodenal curve as age advances. The most fixed point of the duodenum is the duodenojejunal flexure, opposite lumbar 2 ± 1 vertebra. It does not migrate with age. In accordance with the state of fulness of the stomach and duodenum, postural changes may induce an excursion of the duodenum of about ±2 vertebrae.

Four cases of redundancy of the first part of the duodenum simulating duodenal ulcer or pseudodiverticulum are reported.[293]

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290. Machella, T. E.; Hodges, H. H., and Lorber, S. H.: The Restoration of Gastric Motility by Urethane of B-Methyl Choline After Section of the Vagus Nerves for Peptic Ulcer, Gastroenterology **8**:36-51, 1947.

291. Hollander, F.: The Insulin Test for the Presence of Intact Nerve Fibers After Vagal Operation for Peptic Ulcer, Gastroentrology **7**:607-614, 1946.

292. Friedman, S. B.: The Position and Mobility of the Duodenum in the Living Subject, Am. J. Anat. **79**:147-165, 1946.

293. Slater, I. H., and Lautkin, A.: Redundant Duodenum, U. S. Nav. M. Bull. **46**:1651-1657, 1946.

Experimental Duodenal Pouch.—Sonnenschein, Grossman and Ivy [294] describe a method for the production of a chronic, denervated duodenal pouch in the dog. The transplanted duodenal pouch responds to the ingestion of a meal by an increased rate of secretion lasting several hours. The pouch responds to the intravenous injection of a relatively crude intestinal mucosal extract containing secretin but much less to the injection of pure secretin. It is concluded that the secretion of the duodenum is probably in greatest part produced by Brunner's glands and that the volume of the secretion is regulated by a humoral mechanism. This hormone is to be found in a crude secretin product, but it is not secretin.

Septum.—A congenital septum located in the third portion of the duodenum produced an enormously dilated duodenum and obstructive symptoms, which were relieved by duodenojejunostomy.[295]

Aberrant Pancreas.—Aberrant normal pancreatic tissue was found at autopsy in the wall of the duodenum in a patient who was the victim of an accidental death.[296] Three similar lesions had been reported previously by Whipple in a series of two hundred and fifty-seven duodenal lesions other than ulcer.

Diverticula.—Obstructive jaundice resulted from inflammation of a primary diverticulum located at the ampulla of Vater, with secondary inflammation of the biliary tract.[297] An instance of benign ulceration within a diverticulum of the fourth portion of the duodenum is described;[298] the symptoms were controlled by a strict ulcer regimen, and subsequent roentgen examination demonstrated healing of the crater.

Ulcer of the Fourth Portion.—An ulcer of the fourth portion of the duodenum was demonstrated at operation on a 61 year old housewife, who had episodes of epigastric pain and hematemesis for six years.[299] The free acidity after an alcohol test meal was 121 clinical units.

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294. Sonnenschein, R. R.; Grossman, M. I., and Ivy, A. C.: The Humoral Regulation of Brunner's Glands, Acta med. Scandinav. (supp. 196) **128**:296-307, 1947.

295. Lamson, O. F.: Duodenal Septum, West. J. Surg. **54**:384-389, 1946.

296. Norris, J. C.: Aberrant Pancreas in the Duodenum, South. M. J. **39**: 549-551, 1946.

297. Goñi: Diverticulo primario del duodeno su asociacion con icteria, Rev. Assoc. med. argent. **60**:803-806, 1946.

298. Weig, C. G.: Benign Ulceration Within a Duodenal Diverticulum, Radiology **48**:143-147, 1947.

299. Culver, G. C.; Frawley, T. F., and Goade, W. J.: Benign Ulcer of the Fourth Portion of the Duodenum, Am. J. Roentgenol. **57**:333-337, 1947.

300. Cave, W. H.: Duodenal Injuries, Am. J. Surg. **72**:26-31, 1946.

Injuries.—In an analysis of 118 cases of duodenal injuries sustained in World War II, Cave [300] reports a mortality during the first ten days of 55.9 per cent (the mortality in the 10 cases reported in World War I was 80 per cent). Seventy-one per cent of the deaths occurred in the first three days; shock and hemorrhage accounted for 39 deaths, pneumonia 9, anuria 8, peritonitis 3, transfusion reaction 2 and pulmonary embolism 1. The cause of death was unrecorded in 4 cases. Multiple complicating injuries were usually present; vascular injuries were common. Transection of the duodenum occurred in 20 patients; complicating fistula developed in 2 known cases and probably in others. Most of the injuries were repaired by end to end anastomosis.

Cysts.—A congenital enterogenous cyst of the duodenum in a 12 year old boy was removed surgically.[301]

Malignant Tumors.—Dixon and others [302] report a series of forty-nine neoplasms of the duodenum, exclusive of lesions of the ampulla of Vater. Obstructive features were present in 38 cases, while in 6 anemia resulting from loss of blood was the chief finding. The operative mortality was 22 per cent for the 45 patients subjected to operation. A primary carcinoma of the duodenum is recorded by Rossi.[303]

(To be concluded)

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301. Shallow, T. A.; Wagner, F. B., Jr., and Manges, W. B.: Enterogenous Cysts of the Duodenum, Surgery **21**:532-540, 1947.

302. Dixon, C. F.; Lichtman, A. L.; Weber, H. M., and McDonald, J. R.: Malignant Lesions of the Duodenum, Surg., Gynec. & Obst. **83**:83-93, 1946.

303. Rossi, R. A.: Cancer primitivo del duodeno, An. Fac. de cien. med. de La Plata **13**:393-408, 1947.

Book Review

Practical Emulsions, Including a Symposium on Emulsifying Agents and Emulsions in Industry. By H. Bennett, M.D. Second edition. Price, $8.50. Pp. 568. Brooklyn: The Chemical Publishing Company, Inc., 1947.

This book is chiefly concerned with emulsion technology as applied in industry. It is divided into three parts, comprising several chapters each.

In part I a brief nontechnical discussion is given of the theory of emulsion formation, emulsifying agents, stability of emulsions, dispersing agents and wetting agents, concluding with an extensive list (963) of commercial surface-active agents and their chemical nature which in many instances includes a patent number. A list of demulsifying and defoaming agents is also given.

Part II is a symposium by several authors on specific emulsifying agents. Several of these might be of interest to the physician because of their use in food or medicinal preparations. These include the use of lecithin in the preparation of margarine, doughs from certain types of flour, cosmetic creams, chocolate preparations, etc. The section on surface-active agents as germicides includes a description of such compounds as "zephiran chloride," "phemerol," "ceepryn" and "emulsion 607." These act at high dilutions on specific micro-organisms, have a relatively low toxicity index and have been extensively applied in gynecology, ophthalmology, dermatology and dentistry.

Part III contains formulas in which emulsifying agents are used. These apply to such materials as food emulsions, medicinal preparations, cosmetics and drugs, paints, polishes, textile emulsions, sizings, rot-proof and water-proof materials, cleaners' soaps, antiknock fuels, solidified gasoline and agricultural sprays.

From the foregoing, it is apparent that while this book is unique as a source of practical information on surface-active compounds its interest to the physician is limited to those sections concerned with foods, cosmetics and germicides.

Nogle respirationsfysiologiske undersogelser ved lungetuberkulose: Thoracoplastikkens indflydelse paa lungevolumen den alveolaere ventilation belyst ved fractioneret alveoleluftanalyse. By Ulf Gad. Pp. 159. Copenhagen: G. E. C. Gads Forlag, 1941.

This monograph, written in Danish with an English summary, presents studies in preoperative and postoperative lung volumes and composition of alveolar air on patients with pulmonary tuberculosis subjected to thoracoplasty. The first of three chapters deals with the effect of thoracoplasty on lung volume in 51 subjects. Vital capacity was determined spirometrically and compared with results derived from West's formula. Residual air was determined by the hydrogen dilution method. Patients with tuberculosis usually had lowered total capacities and often relatively high residual fractions preoperatively. Postoperatively, the vital capacity was further reduced, but in 24 per cent the residual air was increased. He found patients to be dyspneic on exertion if vital capacity was less than half of the calculated normal amount. Incidentally, the use of roentgenologic planimetry in estimation of lung volume was found unreliable because of wide individual variation.

The second chapter gives the extremely variable results of testing 78 patients for "mixing capacity" after the manner of Lundsgaard and Schierbeck.

The last chapter reports fractional gas analyses on expired and alveolar air both preoperatively and postoperatively with the use of Sonne and Nielsen's apparatus after single inspirations of pure hydrogen. Hydrogen content on expiration decreased more rapidly than normally, and the rate of decrease varied with the severity of the pulmonary tuberculosis. On the other hand, since oxygen values in expired air were more nearly normal in these subjects, the author assumes that blood flow must have decreased in the poorly ventilated parts of the lungs (62 patients).

The author concludes that dyspnea in his patients was due to changed lung volumes and to disturbed alveolar ventilation and that dyspnea might have been worse but for compensating alterations in alveolar blood perfusion. Ingenious charts are included.

Since this work was published, direct measurements of ventilation capacity have shown that vital capacity taken alone can be no criterion of ventilation. Gray, Cournand and others have further clarified the subject of pulmonary function, developing and applying clinically useful tests in studies made on normal and on diseased subjects.

This study is one of the first to compare strictly preoperative and postoperative testing in large series of cases of thoracic disease requiring surgical treatment; it deserves the attention of those who are interested in respiratory physiology and in thoracic diseases.

Advances in Internal Medicine. Edited by W. Dock and I. Snapper. Volume 2. Price, $9.50. Pp. 642. New York: Interscience Publishers, Inc., 1947.

The second volume of this series contains sections on electrocardiography, circulatory failure, angiocardiography and angiography, surgical treatment of hypertension, surgical treatment of tumors and chronic inflammation of the lung, insecticides, physiologic and medical aspects of aviation and deep-sea diving, penicillin in subacute bacterial endocarditis and other infections, Rhesus antigen, pernicious anemia and other megaloblastic anemias, nutritional requirements in disease and nutritional diseases in the Orient.

The section on electrocardiography is excellent in presentation and illustration. Since there is no other readily available source of all the material presented, this volume becomes more valuable. In the section on circulatory failure the author's concepts are presented. Numerous charts add to the clarity of the presentation. Some of the ideas are controversial.

In the section on angiocardiography the method and clinical applications of contrast visualizations are discussed. The illustrations are well chosen and as a whole are well reproduced. The accompanying diagrams add clarity to the few plates which lack contrast.

The surgical treatment of hypertension is reviewed from the standpoint of anatomy of the sympathetic nervous system, purpose, indications and contraindications and evaluation of results of sympathectomy. The various operative procedures are compared.

The surgical approach to bronchial adenoma, bronchogenic carcinoma, tuberculosis, bronchiectasis and lung abscess is briefly reviewed.

The effectiveness, the methods of application and the toxicity of various insecticides are presented. The greater part of the section is devoted to a discussion of DDT (dichlorodiphenyltrichloroethane).

The two sections on the use of penicillin present concise information on the assay, use, indications, dosage and methods of administration of penicillin. The material presented and an extensive bibliography make these sections extremely valuable.

Although the reviewer would like to have included other "advances" in internal medicine, this volume is recommended.

Experimental Catatonia: A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology. By Herman Holland de Jong, M.D. Price, $4. Pp. 225. Baltimore: Williams & Wilkins Company, 1945.

The experimental production of catatonia in animals by the use of bulbocapnine was first described by the author and Baruk in 1930. The present book represents an extension and an expansion of that significant research. A variety of substances are now known to produce catatonic signs. The first part of this book consists of detailed and extensive protocols of numerous experimental studies. Catatonia was induced by means of drugs, asphyxiation, centrifugation, surgical occlusion of the carotid arteries, audiogenic stimulation and other methods.

The implications for human pathology, with particular reference to catatonic schizophrenia, are presented in the second part of the book.

Dr. de Jong concludes that experimental catatonia is analogous to epileptiform seizures in that both conditions represent nonlocalized diffuse reactions of the central nervous system. He offers the suggestion that cellular asphyxiation may be responsible for the onset of catatonic signs.

He believes that schizophrenia is primarily an organic disease, the mental symptoms being secondary phenomena. He cautiously suggests that there may be a toxic etiologic agent in this disease since "only alterations of the function of the liver and the intestine proved capable of producing experimental catatonia," lesions of the other organs having no such effect. Abnormal reactions to liver function tests by catatonic schizophrenic patients suggested the possibility of primary hepatic damage resulting in the formation of a toxic protein metabolite which may produce cellular anoxia in the nervous tissues and resultant catatonic signs.

This book is skilfully written and authoritative, and it represents stimulating research by an internationally known scientist. It should be of great interest to physicians and to research workers concerned with the physiologic approach to the baffling problem of the etiology of schizophrenia.

Hospital Care in the United States. By the Commission on Hospital Care. Price, $4.50. Pp. 631. New York: The Commonwealth Fund, 1947.

This royal octavo volume of 630 pages embodies the studies of hospital care in the United States made by the Commission sponsored by the Commonwealth Fund. The obviously correct assumption having been made that hospital care in the United States is inadequate, a huge amount of factual material is assembled in support of this position. Along with this, elaborate recommendations are made, and these are stated in section II in the form of 181 classified propositions. The reviewer is a little uncertain about the categorical way in which some of these propositions are set down. Being himself neither a sociologist nor a statistician but a teacher of medicine, he has scanned closely propositions 50 to 55, which concern medical education. He feels that these propositions at least are somewhat inadequate from the standpoint of the relation of medical education to hospital

service. Indeed, in discussions of this sort it must be clearly realized that the university teaching hospital serves a purpose so entirely different from that of nonteaching hospitals devoted mainly to patient service that the two can hardly be discussed at all under the same heading. It would also have been interesting to have a fuller discussion of the impact of the specialty boards on hospital staffs.

The book is far too comprehensive, however, for a brief review. As a storehouse of factual information it is certainly invaluable, and most of the recommendations are sound and constructive or at least serve as a good starting point for further discussion. This study is beyond question a necessary and outstanding contribution to progress in the field, and its sponsors are to be warmly congratulated.

Internal Medicine in General Practice. By Robert P. McCombs, M.D. Second edition. Price, $8. Pp. 741, with 122 illustrations. Philadelphia: W. B. Saunders Company, 1947.

The first edition of this text was reviewed favorably in the ARCHIVES in 1943. The revised second edition is a satisfactory work which this reviewer would be pleased to use for teaching senior medical students. The arrangement of the material is unusual for the major approach to disease states is through symptomatology rather than through morbid anatomy. The first two chapters, "Fundamentals of Diagnosis" and "Psychiatric Disorders," are well done and serve a useful function in a textbook of general medicine, since attention is directed sharply to the methods and difficulties of diagnosis. Throughout the book the author emphasizes the necessity of early, accurate diagnosis. In addition to the new material on psychiatric disorders, there is a new chapter on vascular disturbances of the extremities. The comments on therapeutic agents and diagnostic procedures have been revised and include appropriate up-to-date material. The style is pleasantly conversational and easy to read. Inevitably, it has been necessary for the author to be dogmatic in the effort to simplify the material, but his views are generally sound and acceptable. The index is adequate, and the illustrations are well chosen and well reproduced. Unfortunately the typography is not always clear due to faulty alinement of letters. This book should be useful to the general practitioner and to others who want a modern, thorough and convenient text on internal medicine.

Jaundice: Its Pathogenesis and Differential Diagnosis. By Eli R. Movitt. Price, $6.50. Pp. 261. London: Oxford University Press, 1947.

The question of what is the trouble with the patient suffering from jaundice is a fairly common one in medical practice. Is the primary lesion in the blood or in the liver or the bile ducts, and if there is obstruction in the bile ducts, is this due to a stone or is it due to a carcinoma around the papilla? Usually an expert in this field of diagnosis can give the answer, and in many cases he can warn the surgeon that he had better not operate since there is little chance of his doing any good and there is a big chance that the shock of the operation will bring the patient's life to a close.

In this book Movitt has gathered together an enormous amount of information relating to jaundice and to what is known today about the diagnosis of the several types of disease. Every internist and gastroenterologist would do well to read this book and to keep it handy near his desk. It begins with chapters on the anatomy and physiology of the liver and the biliary tract and on the metabolism

of the bile pigment. Then follow chapters on the pathogenesis of jaundice, diagnostic procedures and modes of differential diagnosis. Other chapters are on hemolytic jaundice, parenchymatous jaundice with acute, subacute and chronic hepatitis and carcinoma involving the liver. The final chapter is on obstructive jaundice.

The book is well and interestingly written and can be heartily recommended.

Maladies et syndromes rares ou peu connus. By A. Aimes, M.D. Pp. 208, with 26 illustrations. Paris: Masson & Cie, 1946.

As the title of this monograph indicates, most of the rare medical syndromes are discussed. The syndrome is defined and the characteristics summarized. It is an extremely useful book.

The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities. By Philip Lewin, M.D. Third Edition. Price, $11 (buckram). Pp. 847, with 389 illustrations. Philadelphia: Lea & Febiger, 1947.

Whether it is logical to assemble in one massive book everything to be known about the foot is an interesting question for discussion. For example, should arthritis of the foot be discussed in a book on arthritis or in a book on the foot? Do the circulatory disturbances in the foot belong under the same covers with bunions or are the latter best dealt with in an orthopedic treatise? Be this as it may, Dr. Lewin's book is now in its third edition, so that there is evidently a place for topographic medicine of this sort. The volume is a handsome one, well and profusely illustrated, and there is a lengthy bibliography. The reviewer is glad to have the book on his shelves.

Advances in Pediatrics. Edited by S. Z. Levine, A. M. Butler, L. E. Holt, Jr., and A. A. Weech. Volume 2. Price, $6.75. Pp. 409. New York: Interscience Publishers, Inc., 1947.

Eleven timely, well written and carefully chosen articles make up the attractive second volume of this book. The contributors, all active workers and acknowledged authorities in selected fields, have condensed and summarized each subject to a remarkable degree. All contributions are organized and set up in a most useful and readable form; the bibliographies are excellent. Helping to bridge the gap which unfortunately must always exist between current publications and textbooks, such a volume will certainly be useful to all workers in this and allied specialties.

Osteotomy of the Long Bones. By Henry Milch, M.D. Price, $6.75. Pp. 294. Springfield, Ill.: Charles C. Thomas, Publisher, 1947.

This interesting book adequately fulfils the author's stated purpose of summarizing the principles of the various types of osteotomy for the general surgeon. The work is not an exhaustive review which might interest particularly the orthopedic surgeon, but the author does bring into the volume a summary of the various types of osteotomy which have gradually been developed for the correction of deformity and the improvement of function.

For the most part, the book provides interesting reading which is easily understood, but included also are several sections of mathematical equations which make

dull reading and are difficult of interpretation by the average reader. It is impossible to express any mathematical formula which will apply in each case, and even if such were possible, the application of an exact formula would be impossible of fulfilment at the operating table.

Aside from the weighty sections on mathematics, the book may be recommended for an over-all picture of the use of osteotomy. The author is to be commended for his study and presentation of a single type of operation which has several varied applications. The book is well planned, the illustrations are exceptionally clear and sufficient reports of cases are given to lend support to the text.

Kompendium der parasitischen Wurmer in Menschen. By Hans A. Kreis, M.D. Pp. 133, with 70 illustrations. Basel, Switzerland: Benno Schwabe & Co., 1947. Distributor in United States, Grune & Stratton, Inc., New York.

This little book makes no claim to originality. The author states that there is no similar compendium in the German language, and he has compiled this manual from a variety of sources. Points of note are the excellent illustrations, the key table to the identification of parasites and ova and the good paper and print. The book should have a wide use in countries in which German is spoken.

Trichomonas Vaganalis and Trichomoniasis. By Ray E. Trussell, M.D., with an Introduction by E. D. Plass, M.D. Price, $6. Pp. 288. Springfield, Ill.: Charles C Thomas, Publisher, 1947.

Although the subject of the trichomonas organism would on first thought hardly seem to justify a whole book, it certainly is useful to find between two covers all that is known to date about the biology and the disease-producing capacities of this interesting flagellate. The author has assembled a bibliography of 1,586 titles, and there is a critical discussion of over one hundred agents which have been claimed to be of value in Trichomonas vaginalis infections.

Synopsis of Allergy. By Harry L. Alexander. Second edition. Price, $3.50. Pp. 255. St. Louis: The C. V. Mosby Company, 1947.

For a small book, the "Synopsis of Allergy" (second edition) presents an excellent review of present day opinions regarding allergic diseases and the more important causes, diagnostic methods and treatment. It should be a valuable addition to any medical library.

The Practical Nurse. By Dorothy Deming, R.N. Price, $3. Pp. 357. New York: The Commonwealth Fund, 1947.

The Commonwealth Fund has again sponsored a most important book. Recent years have clearly shown that the problems of nursing service cannot be adequately handled by the available supply of trained nurses. Hence, the development of practical nurses to supplement the work done by highly trained experts becomes an obvious need. Mrs. Deming's comprehensive study covers the problem of the practical nurse from every standpoint—historical, educational and economic. It is a book which will be essential to all dealing with problems of nursing service as well as a landmark in the philosophy of nursing education.